COGNITIVE FUNCTIONING IN FIBROMYALGIA

By

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Fibromyalgia (FM) is a musculoskeletal disorder characterized by widespread chronic muscular pain. Many people with FM report cognitive deficits, including poor memory and concentration abilities and difficulties with word finding. However, only a few studies have investigated cognitive functioning in FM.

Previous studies have reported that FM subjects display attentional and memory deficits. However, these studies failed to take into account the possible effects of medication on cognitive performance. In the current study, measures of language (Boston Naming Test, animal fluency, and letter fluency), attention [Paced Auditory Serial Addition Task (PASAT) and the Auditory Consonant Trigrams (ACT)], and memory (California Verbal Learning Test, Rey Osterrieth Complex Figure, and the Information subtest of the Wechsler Adult Intelligence Scale-Revised) were given to 24 FM subjects diagnosed according to American College of Rheumatology criteria. The FM group's performance was compared to 24 age- and education-matched healthy controls who were screened for psychiatric illness. In addition to the cognitive measures, tests of severity of illness (the SF-36 Health Survey), mood (Profile of Mood States), and FM symptomatology (using visual analogue scales) were given.

No significant correlations were found between the cognitive measures and the severity of illness, mood, or pain measures in the FM group. Also, no significant differences were found between nondepressed, medication-free FM subjects and healthy controls on any of the cognitive measures. Thus, it does not appear that the disease process itself causes cognitive deficits in FM. However, FM subjects on antidepressant medication performed significantly worse than controls on the letter fluency task and the ACT. This analysis was completed on nondepressed FM subjects to remove the confounding effects of depression. Also, no differences were found in pain level between medicated and unmedicated subjects. Thus, it appears that FM patients who complain of cognitive deficits may be those who are taking antidepressant medication. Because no subjects were depressed but nonmedicated, it was impossible to measure the effects of depression on cognition in FM without the confounding effect of medication. The results of this study suggest that medication use must be taken into account when measuring cognitive functioning in this population.

CHAPTER 1
INTRODUCTION AND LITERATURE REVIEW

Fibromyalgia (FM) is a musculoskeletal syndrome characterized by widespread chronic pain that is particularly intense at specific anatomical sites known as tender points (Wolfe et al., 1990; Yunus, Masi, Calabro, Miller, & Feigenbaum, 1981). It is associated with sleep disturbance, fatigue, morning stiffness, headaches, paresthesias, and depression, and these symptoms are aggravated by cold weather, poor sleep, humidity, stress, anxiety, and weather changes. FM is a frequently misdiagnosed condition that can cause considerable disability in individuals who are afflicted with the illness (Yunus, Masi, & Aldag, 1989).

FM occurs in people of different race, age, nationality, and sex (Doherty & Jones, 1995; Wolfe et al., 1990; Wolfe, Ross, Anderson, Russell, & Hebert, 1995), although nearly 90% of cases are women. Wolfe et al. (1995) studied the prevalence and characteristics of the syndrome and found that approximately two percent of the general population has FM. Among women, it is most common in the 50 and above age group. Ten to 20 percent of new patients presenting at rheumatology clinics are diagnosed with this syndrome (Wolfe, 1989).

The purpose of the present paper is to describe cognitive functioning in individuals with FM. In Part 1 of the Introduction, the manner in which FM is diagnosed will be presented first, followed by a description of the primary symptoms associated with the disorder. Next, the pathophysiology of FM will be discussed, including the notion that FM is a central nervous system (CNS) disorder. How these pathophysiological findings relate to the symptoms of the disorder will then follow.

In Part 2 of the Introduction, the impact that the CNS abnormalities involved in FM have been shown to have on cognition in other populations will be presented. This literature will indicate that cognitive difficulties would be expected in FM due to the areas of CNS that are implicated in the disorder. In Part 3 of the Introduction, the few studies that have examined cognitive abilities in FM will be discussed. Finally, Part 4 will include a brief summary of the literature along with the proposed hypotheses for the current study.

Part 1: Diagnosis, Symptoms, and Pathology of Fibromyalgia

The Diagnosis of Fibromyalgia

The etiology of FM is still unknown, and, as yet, there are no laboratory tests available for its diagnosis (Yunus, Masi, & Aldag, 1989). In 1990, the American College of Rheumatology (ACR) developed criteria for the classification of fibromyalgia (Wolfe et al., 1990). Prior to this, no uniform diagnostic criteria were available, yet several similar methods of classification were used (Smythe & Moldofsky, 1977; Wolfe, Hawley, Cathey, Caro, & Russell, 1985; Yunus et al., 1981, 1989). FM is now diagnosed when patients present with a three month or longer history of widespread pain involving all four quadrants of the body. Pain must also be present on digital palpation at 11 or more of 18 designated tender points. Associated symptoms need not be present for a diagnosis to be made, but their presence aids in the diagnosis. For example, sleep disturbance, fatigue, and stiffness occur in 75% of FM patients.

Fibromyalgia was formerly called fibrositis, a term first used by Sir William Gowers in 1904 (Gowers, 1904). Because no evidence of inflammation has been found in patients with FM (Yunus et al., 1981), this term has been replaced with the term FM, meaning pain in the muscles (Jacobsen, 1994). In the past, patients with FM were sometimes diagnosed with psychogenic rheumatism because these individuals presented with chronic pain in the absence of known organic pathology (LaFratta & Porterfield, 1961). More recently, the question of whether or not FM is a variant of depression has been addressed by several authors. In the next section, the primary symptoms of the disorder will be described, including depression and anxiety, sleep disturbance, and pain.

Primary Symptoms of FM

Depression and anxiety

Depression is commonly reported in FM. Ahles, Yunus, Riley, Bradley, and Masi (1984) examined psychological factors in 45 patients with FM, 30 patients with rheumatoid arthritis (RA), and 32 normal controls. Psychological tests administered included the Minnesota Multiphasic Personality Inventory (MMPI; Dahlstrom, Welsh, & Dalhstrom, 1972), a measure of life stress called the Holmes-Rahe Life Events Inventory (Holmes & Rahe, 1967), and the Bakker Assertiveness-Aggressiveness Inventory (Bakker, Bakker-Rabdau, & Breit, 1978), which measures social skills. The patients' MMPI profiles were divided into types, as has been done when examining MMPI performance in chronic pain patients (Armentrout, Moore, Parker, Hewett, & Feltz, 1982; Bradley, Prokop, Margolis, & Gentry, 1981). Group 1 consisted of those with no MMPI scales greater than 70 and was called the normal subgroup; Group 2 had T-score elevations on Hs (Hypochondriasis), D (Depression), and/or Hy (Hysteria) and was designated the typical chronic pain group; and Group 3 had T-score elevations greater than 70 on four or more scales, and was termed the psychologically disturbed group.

According to Bradley, Prokop, Gentry, Van der Heide, and Prieto (1981), the profile of Group 2 is typical of patients with chronic pain. The Hs, D, and Hy scales contain several items related to physical symptoms, which would tend to be endorsed frequently by patients with chronic pain. As pain becomes chronic in an individual, vegetative signs of depression and hypochondriasis become evident, such as sleep disturbance, irritability, and somatic preoccupation (Bradley et al., 1981). This would be reflected in the elevation of these three MMPI scales.

Ahles et al. (1984) found that patients with FM scored significantly higher than normals on all 8 clinical scales and significantly higher than the RA patients on four of them (Hs, Hy, Pt [Psychasthenia], and Sc [Schizophrenia]). The RA patients scored higher than normals on the Hs, D, and Hy scales, the pattern which is typically seen in patients with chronic pain (Bradley et al., 1981).

Approximately equal numbers of patients with FM had MMPI scores that fell within each of the three subgroups described above, while most of the RA patients were in Group 1 (45%) or Group 2 (48%). Significantly more RA patients' scores fell within Group 2 as compared to the normal controls, who were placed mostly into Group 1 (88%). FM patients were found to have significantly more life stresses than the RA and normal groups, but no differences were found among the three groups in social skills. The FM subgroup deemed psychologically disturbed reported the greatest number of life stresses, suggesting that their psychological symptoms may have been related to the experience of multiple stressful events. The fact that FM patients were found to have experienced more stress in their lives supports the notion put forth by several authors that FM is brought on or perpetuated by stress (i.e., Sternberg, 1993; Yunus, 1992).

Thirty-three percent of the FM patients had profiles that are typically seen among patients with chronic pain, including those with disorders for which there is a definite organic etiology, and one-third of the FM group displayed no depression or other psychological symptoms. Thus, two thirds of the FM patients in this study exhibited no depression or other psychological symptomatology, or had symptoms that would typically be expected as a reaction to living with a chronic illness. Therefore, the authors concluded that psychological factors appear to occur in some patients with FM, but only a subset of patients exhibit severe disturbance.

Wolfe et al. (1984) also compared MMPI profiles of FM patients to those with RA, and separated scores into the same groups described in the Ahles et al. (1984) study. Here, too, FM patients were evenly distributed across the normal, somatically concerned, and psychologically disturbed groups. Sixty percent of the RA patients exhibited normal profiles, 23% fell into the typical pain profile group, and 16% were considered to be psychologically disturbed. An index of anxiety and depression, the Arthritis Impact Measurement Scale (Meenan, Gertman, & Mason, 1980), and a measure of self-motivation, the Motivation Scale (Dishman & Ickes, 1981) were also given. FM patients displayed significantly higher anxiety and depression, but showed same levels of self-motivation as the RA group.

Not all studies have found psychological differences between FM patients and other medical patients. For example, Clark, Campbell, Forehand, Tindall, and Bennett (1985) examined depression and anxiety in 22 FM patients and 22 medical patients without FM. These subjects were selected from 596 patients attending a general medicine and medical subspecialty clinic. The 596 patients were asked to complete a questionnaire concerning musculoskeletal symptoms. Forty-two patients who were suspected of having FM were further evaluated, and of these, 22 were diagnosed with FM but had no concurrent illness. Twenty-two age-, sex-, race-, and clinic-matched patients without FM were also selected. All 44 subjects were then given the Beck Depression Inventory (BDI) (Beck, 1978), the Spielberger State and Trait Anxiety Inventory (STAI; Spielberger, Gorsuch, & Lushene, 1970), and the SCL-90-R (Derogatis, Lipman, Rickels, Uhlenhuth, & Covi, 1974), which is a self-report measure of current physical and psychological symptoms, including depression and anxiety. No differences were found between the FM and control groups on any of the measures. Clark et al. (1985) concluded that psychological factors do not play an important role in the perpetuation of FM. They also suggested that other studies have found greater psychological distress among FM patients because subjects were recruited from rheumatology clinics rather than from general medical settings. Rheumatology patients, they argued, may have more severe cases of the disorder and may have been referred because they were not responding to treatment by a general physician. Because this study screened a general medical population, patients may have been selected who had more mild cases of FM or who had been sick for a shorter period of time, and in turn, may have been experiencing less psychological distress.

These authors also suggested that a greater incidence of psychological symptoms in FM than in RA may have been found because of the consistent uncertainty that is expressed to FM patients by their doctors, family members, and society about the nature, or even existence, of their illness. This, they suggested, would cause an increase in psychological distress above what would be expected for individuals experiencing their level of disability.

A study by Martinez, Ferraz, Fontana, and Atra (1995) examined depression in FM and determined the temporal relationship between the onset of pain and the appearance of depression. They found that in 40 percent of depressed FM patients, depression had preceded the onset of the disorder; twenty-four percent reported that depression occurred at the onset of FM; and the rest of the subjects developed depression following the onset of FM. This study suggests that depression may somehow play a role in the development of FM in some patients, but that it is not a clear etiological factor in all patients.

Thus, it appears that FM is associated with psychological symptoms in some patients, but that the extent to which psychological factors are involved in the onset or perpetuation of the illness is unclear. The Clark et al. (1985) study suggests that depression may occur moreso among patients who are more severely disabled. The research does not indicate that depression is a clear etiological factor in the development of the disorder, and thus, the notion that FM is a form of psychogenic rheumatism is not likely warranted. As LaFratta and Porterfield (1961) stated, the coexistence of emotional disturbance and physical symptoms is not proof of psychogenic origin of the symptoms, even when organic pathology cannot be found.

Sleep disorder

In addition to depression and anxiety, patients with FM frequently present with a sleep disorder. Moldofsky, Scarisbrick, England, and Smythe (1975) have described this sleep disturbance as an abnormal presence of alpha rhythms in the nonrapid eye movement (NREM) stages of sleep, which can be seen on electroencephalogram (EEG) recordings. Normal sleep consists of two stages: NREM sleep and rapid eye movement (REM) sleep (Tortora & Anagnostakos, 1987). NREM sleep, also called slow wave sleep, consists of four progressively deeper stages, each of which normally merges into the next. During Stage 1, alpha (waking) waves diminish on the EEG, and then theta waves appear; the EEG of Stage 2 shows sleep spindles; Stage 3 involves sleep spindles and delta waves; and Stage 4, during which deep sleep occurs, is dominated by delta waves. REM sleep, also known as paradoxical sleep, is similar to NREM Stage 1 sleep. In FM, EEG activity that is characteristic of wakefulness often occurs during NREM Stage 4 (or deep) sleep.

Moldofsky et al. (1975) obtained EEG recordings from 10 untreated patients with FM. The first night's results were discarded to allow for adjustment to sleeping in the laboratory. All subjects displayed an overnight increase in pain and a coincident NREM EEG sleep disturbance. In seven of the subjects, NREM Stages 2-4 were contaminated by alpha wave intrusions. The remaining three patients had no Stage 4 sleep and no, or very little, Stage 3.

In the same study, Moldofsky et al. (1975) deprived healthy nonathletic control subjects of Stage 4 sleep. When subjects began to enter Stage 4 sleep, a buzzer was sounded until the EEG showed clear signs of arousal and a shift to Stage 1 or 2. After three nights of no Stage 4 sleep, these subjects developed temporary muscle pain and mood symptoms (depression and irritability) comparable to the patients with FM. These symptoms disappeared once normal sleep was resumed. This study shows that NREM Stage 4 sleep is disrupted among patients with FM, and that this stage of sleep may be associated with some sort of restorative function involving the muscles and mood. The fact that the normals developed depressed mood as a result of lack of Stage 4 sleep is of interest because this suggests that depression in FM could relate, at least in part, to the lack of sleep that occurs with this illness.

Chronic pain

In addition to disrupted sleep and psychological distress, pain is another symptom associated with FM. Muscle pain, often involving muscle spasms, is evident, and this pain is reported to increase following exercise (Jacobsen, 1994). Stiffness and joint pain occur in about 90% of FM patients, especially upon rising in the morning. Approximately half of patients report headaches, which may be caused by muscle tension. Also, paresthesias, or any type of abnormal sensation such as burning, numbness and tingling (Dox, Melloni, & Eisner, 1985), are present in anywhere from 26% to 84% of FM patients. Possible causes of muscle pain in FM will be discussed in later sections.

Although the etiology of FM has not yet been determined, several recent pathophysiological findings may explain the symptoms of the disorder. These findings suggest that FM involves CNS dysfunction. In the next section, pathophysiological abnormalities that have been discovered among patients with the disorder will be presented, followed by a discussion of the role that these abnormalities may play in the symptoms of FM.

Pathophysiological Findings in FM

Low regional cerebral blood flow

Two studies have shown that people with FM demonstrate decreased blood flow in the brain. Mountz et al. (1995) measured regional cerebral blood flow (rCBF) in the cortex, thalamus, and head of the caudate nucleus in 10 untreated women with FM and in 7 age- and education-matched normal controls. All patients met ACR criteria for FM. Resting-state rCBF was measured using single-photon-emission computed tomography (SPECT). Because depression occurs in some patients with FM, which could affect SPECT results, a measure of depression, the Center for Epidemiological Studies Depression Scale (CES-D; Radloff, 1977), was completed by the subjects. The STAI was also administered to both groups to measure anxiety. Pain threshold assessments were performed in which subjects were asked to rate their pain on a 7-category rating scale.

Patients with FM were found to have significantly lower pain thresholds than controls. They demonstrated significantly higher depression scores on the CES-D and significantly higher scores on the anxiety measure. Significantly lower rCBF in the left and right thalamus, the left and right heads of the caudate, and across the anterior, lateral, and posterior cortex, as compared to other structures in the brain and as compared to controls, was found in FM subjects. Computed tomography (CT) scans were normal, and thus no morphological abnormality could likely account for the hypoperfusion. No significant correlations were found in either group between rCBF in the thalamus or caudate nucleus and age, education level, anxiety, or depression. There were also no significant correlations between rCBF in the three cortical sectors and education, anxiety, or depression. Age, however, was negatively correlated with rCBF in the cortex among all subjects.

Because depression has been associated with low blood flow in the cortex (Schwartz et al., 1994), depression might have accounted for the low rCBF in this study. However, no correlations between depression scores and rCBF to this area were found. Depression has not been associated with lower rCBF in the caudate nucleus and thalamus in other studies (i.e., Schwartz et al., 1994), and was not related to low rCBF in these areas in this study. Thus, low rCBF in this study may reflect the underlying pathology involved in FM.

McDonald-Haile et al. (1994) used SPECT scans to examine rCBF in the caudate nucleus among patients with chest pain of unknown etiology (CPUE) and patients with FM. CAT scans were performed and measures of depression and anxiety were administered. Both FM and CPUE patients displayed decreased blood flow in both the right and left caudate nucleus as compared to normal controls during a resting state. Anxiety and depression scores were not related to rCBF levels in either group. This study suggests that low blood flow, at least in the caudate nucleus, may be related to chronic pain. Thus, two studies have found low rCBF in several regions of the brain, including the cortex, thalamus, and caudate nucleus, in individuals with FM, and these results do not appear to be related to anxiety or depression.

Low serotonin levels

Further evidence that FM may be a central nervous system disorder has been found from studies examining levels of various neurotransmitters and neurohormones among patients with FM. In particular, these patients appear to have abnormally low levels of serum serotonin. Russell, Michalek, Vipraio, Fletcher, and Wall (1989) measured levels of free plasma tryptophan, the essential amino acid that is a metabolic precursor of serotonin synthesis (Chase and Murphy, 1973), in 20 FM patients diagnosed according to ACR criteria. The FM patients exhibited significantly lower levels of total serum tryptophan as compared to a group of age-, sex-, and race-matched controls. Russell et al. (1992) measured serum serotonin levels and the density of serotonin reuptake receptors on peripheral platelets in 22 untreated patients diagnosed with FM. Blood platelets have been used for many years to investigate serotonin functioning because platelets use serotonin in many ways that are very similar to serotonergic neurons (Grahame-Smith, 1992). Patients were diagnosed according to the criteria of Yunus et al. (1981), which was judged by the ACR to be very similar to their own diagnostic criteria (Wolf et al., 1990). Because depression is also associated with low levels of serotonin (Fowles, 1984), the CES-D and the Hamilton Depression Scale (Hamilton, 1976) was administered to all subjects, including 23 healthy controls. The FM patients exhibited significantly lower concentrations of serum serotonin than healthy controls. Higher densities of serotonin reuptake receptors on platelets were found in the FM group as compared to the controls. Eighteen percent of patients were judged to be depressed on the CES-D, and less than 10 percent displayed probable depression on the Hamilton Depression Scale. No correlation was found between density of reuptake receptors and depression scores. Therefore, the authors concluded that patients with FM have abnormally low levels of serum serotonin and that these results could not be attributed to depression.

Two other studies found evidence of low serotonin levels among patients with FM. Russell, Vaeroy, Javors, and Nyberg (1990) measured 5-hydroxy indole acetic acid (5HIAA), the product of serotonin metabolism in the cerebral spinal fluid (CSF) in 17 FM patients and 12 controls. Individuals with FM were found to have lower 5HIAA levels than the controls. Houvenagel, Forzy, Cortet, and Vincent (1990) also measured CSF 5HIAA levels in FM patients and compared these findings to those of 128 low back pain patients. The FM group again exhibited lower levels than the control group. These two studies may be more valuable than those presented above in that CSF measures of 5HIAA rather than serum levels of serotonin were measured. While it is not certain that serum levels necessarily reflect brain levels of a neurotransmitter substance, it has been demonstrated that amine metabolism in the brain is reliably represented by parallel changes in CSF metabolites (Chase & Murphy, 1973). Therefore, these studies suggest that patients with FM have abnormally low serum and CNS levels of serotonin.

Low growth hormone levels

Adding further support for the hypothesis that FM is a disorder of the CNS is the relatively recent finding that people with FM exhibit abnormally low levels of growth hormone (GH). Bennett, Clark, Campbell, and Burckhardt (1992) measured serum levels of somatomedin C, a GH-related peptide among patients with FM. The authors chose to measure somatomedin C rather than serum GH levels because GH has a very short half-life. Eighty percent of it is secreted during sleep, particularly Stage 4 sleep. Somatomedin C has a half-life of approximately 20 hours, and thus a daytime measurement of it gives a more consistent and accurate measure of GH level than a direct measurement of serum GH. In this study, blood samples were taken from 70 patients with FM, who were diagnosed by ACR criteria, and from 55 age-matched controls. The FM patients had significantly lower levels of serum somatomedin C than controls. No significant correlations were found between somatomedin C levels and scores on a measure of anxiety and depression. Serum somatomedin C levels were also significantly low in 10 patients with FM in a study by Ferraccioli et al. (1994). Griep, Boersma, and de Kloet (1994) and Bagge, Bengtsson, Carlsson, and Carlsson (1998) measured serum GH levels directly over a 24-hour period and found significantly lower levels in 10 patients with FM as compared to a control group. Thus, in addition to abnormally low serum and CNS serotonin levels, FM also appears to be characterized by low serum levels of GH.

Immune system abnormalities

FM may also involve abnormalities within the immune system. Russell, Vipraio, Tovar, Michalek, and Fletcher (1988) examined natural killer cells from FM patients and controls and found significantly lower natural killer cell activity in the patients with FM. Hernanz et al. (1994) found a defect in T cell activation, as compared to controls, in 65 patients with FM.

Others have found abnormal numbers of lymphocyte subpopulations such as elevated T helper cells (Peter & Wallace, 1988; Russell, Vipraio, Michalek, & Fletcher, 1988). Thus, this disorder also appears to be associated with altered immune system functioning.

It is apparent that FM represents a complex syndrome involving decreased rCBF (relative to other structures in the brain) in the thalamus, caudate nucleus, and cortex, abnormally low levels of serotonin and growth hormone, and disturbed immune system functioning. How these findings relate to the symptoms of FM will be discussed next.

Pathophysiological Findings as Related to Symptoms in FM

Low serotonin

Serotonin and sleep dysfunction. Each of the factors described above may involve disruption of complex systems within the CNS that are responsible for the regulation of sleep and the immune system and modulation of pain and mood. Serotonin is involved in all four of these functions. The majority of all serotonergic neurons originate in the raphe nuclei (Nieuwenhuys, Voogd, & van Huijzen, 1988). This group of nuclei is located in the brain stem and is considered part of the reticular formation, a bundle of cells and dendrites that run throughout the brain stem. The serotonergic cells of the brain stem have highly-branched fibers that innervate virtually the entire CNS and are the most extensive neuronal network yet described. The ascending projections of these cells are distributed throughout the midbrain, thalamus, and cerebral cortex, with branches passing through the hypothalamus, internal capsule, amygdala, striatum, and external capsule. Some fibers follow the fornix to the hippocampus. The descending projections innervate the pons, medulla, cerebellum, and spinal cord. Thus, serotonergic projections exist widely throughout the CNS.

Serotonin is thought to be involved in the regulation of sleep. It is known that slow wave sleep is controlled by the raphe nuclei, which are connected to the midbrain reticular center. The reticular center is thought to be involved in producing arousal (Schneider & Tarshis, 1980) and REM sleep (Tortora & Anagnostakos, 1987). Several studies demonstrate the role that the raphe nuclei and serotonin play in the regulation of sleep. For example, when the pontine reticular area is lesioned, desynchronized (REM) sleep is abolished (Riley, 1985). When the raphe area is lesioned in animals and man, slow wave sleep is almost totally abolished, and an inability to sleep occurs (Jouvet, 1969; Riley, 1985). When Parachlorophenylalanine (PCPA), a drug that decreases brain serotonin, is administered to humans, EEG phasic integrated potentials (or spikes that occur during REM sleep) occur increasingly during NREM sleep (Wyatt, 1972). In addition, frequent rapid eye movements, a sign of REM sleep, occur during NREM sleep in PCPA-treated subjects.

The interruption of NREM sleep by waking (alpha) waves in FM suggests that an internal arousal mechanism is in competition with slow wave sleep (Moldofsky et al., 1975). The raphe nuclei are thought to produce NREM sleep by inhibiting activity in the midbrain reticular system. Thus, low serotonergic activity in the raphe in FM may allow for greater activity in the reticular system because the reticular system is disinhibited, thereby producing increased arousal during sleep. Therefore, low levels of serotonin in FM may explain the sleep disorder that is associated with this illness.

In fact, when Fluoxetine, which inhibits neuronal uptake of serotonin in the brain (Guze, Ferng, Szuba, & Richeimer, 1992), is administered to patients with FM, their quality of sleep reportedly improves (Cortet, Houvenagel, Forzy, Vincent, & Delcambre, 1992; Wolfe, Cathey, & Hawley, 1994). This further supports the notion that low serotonin causes disrupted sleep in these individuals.

Serotonin and chronic pain. In addition to causing sleep disturbance, abnormally low levels of serotonin may also be responsible for the pain associated with FM. Serotonin, as well as other neurotransmitter substances, is involved in the mediation of pain. The main sensory pathway for pain is called the lateral spinothalamic pathway (Tortora & Anagnostakos, 1987). Afferent sensory fibers originate from nociceptors, or pain receptors, located in the skin, muscle, and fascia (Yunus, 1992) and ascend in the spinothalamic tract. This tract ascends through the reticular formation of the brain stem and to the ventral posterolateral nucleus (VPL) of the thalamus, before terminating in the somatosensory cortex.

The neurotransmitter substance P (SP) has been found to transmit nociceptive information along the afferent sensory system (Murphy & Zemlan, 1987). Interestingly, this neurotransmitter has been found to be elevated in the cerebral spinal fluid of patients with FM (Russell et al., 1994; Vaeroy, Helle, Forre, Kass, & Terenius, 1988).

Serotonin and norepinephrine appear to mediate analgesia in descending sensory pathways. For example, stimulation of the ventral posterior lateral nucleus of the thalamus in the primate causes a release of serotonin in the spinal cord, resulting in inhibition of spinothalamic tract cells (Yunus, 1992). Yunus (1992) has concluded that pain in FM is due to the effects of abnormally low levels of serotonin and abnormally high levels of SP in the sensory system.

Evidence of the role that serotonin plays in pain comes from another study that employed PCPA. Sicuteri (1972) administered this drug to patients who suffered from migraine headaches. Here, the patients developed symptoms similar to FM, such as pain in the muscles that increased with physical exertion. Symptoms reversed once the drug was discontinued, suggesting that lower levels of serotonin may have been responsible for the muscle pain experienced by the patients. Moldofsky and Warsh (1978) found that level of plasma-free tryptophan was inversely related to severity of pain in 8 FM patients. Animal studies have also demonstrated a link between serotonin and pain. For example, Tenen (1967) administered PCPA to animals that subsequently displayed a decreased jump response threshold to electric shock. The neurochemical and behavioral effects of the drug could be reversed by administering 5-hydroxytryptophan, a precursor of serotonin. Thus, it is conceivable that low serotonin could be related to the pain associated with FM.

Serotonin and depression. Low serotonin has been associated with depression, as has low levels of other neurotransmitters, particularly norepinephrine and dopamine. Some evidence for the role of serotonin in depression comes from the effects of a class of antidepressant drugs called selective serotonin reuptake inhibitors (SSRIs), such as Fluoxetine (or Prozac). These drugs block the reuptake of serotonin into the presynaptic neuron and have been found to successfully treat depression in many individuals (Guze et al., 1992), suggesting that low serotonin is at least one factor involved in depression. When PCPA, which blocks serotonin synthesis, is administered along with antidepressant medication, the antidepressant effect of the medication is lost (Grahame-Smith, 1992). Low levels of 5HIAA in the CSF of depressed patients also supports the theory of serotonin involvement in depression (Thase & Howland, 1995). Finally, low serotonin in the brains of depressed individuals who have committed suicide has also been discovered. Thus, in light of the evidence that serotonin may be involved in depression, it is possible that there is a relationship between low serotonin and depressive symptoms among patients with FM. However, this suggestion is contradicted by the findings of Russell et al. (1992), discussed above, in which the density of serotonin reuptake receptors in patients with FM were not found to be correlated with depression. Thus, it is possible that serotonin levels are not directly related to depression levels in FM.

Low rCBF in the thalamus/cortex

Thalamus and pain. As mentioned earlier, another pathophysiological finding in FM is low rCBF in the thalamus. This finding is not surprising in that the thalamus is involved in the mediation of analgesia in pain. As described above, the main sensory pathway, the lateral spinothalamic tract, projects to the VPL of the thalamus, and stimulation of this area causes the release of serotonin in the spinal cord. The spinothalamic tract also projects to multiple areas of the medial thalamus (Craig, 1987), which is additionally thought to be involved in pain. For example, Bushnell and Duncan (1989) found that some single neurons in the medial thalamus can discriminate changes in the intensity of noxious stimuli.

Stimulation of the ventrobasal thalamus has been found to produce paresthesias among patients with tremors who have had electrodes implanted prior to surgery for treatment of tremor and rigidity (Velasco, Velasco, & Cepeda, 1979). Interestingly, paresthesias are also present in some individuals with FM. Thus, abnormally low rCBF in the thalamus of patients with FM may reflect abnormalities within the ventral lateral posterior, medial, and/or the ventrobasal thalamus, or the projections to these areas, and thus may reflect the pain symptoms that occur in the disorder.

Thalamus/cortex and sleep. Low rCBF in the thalamus and cortex of FM patients may reflect the role these structures play in sleep. As described above, serotonergic neurons from the raphe nuclei project to, and inhibit, cells in the reticular formation of the pons and midbrain (Riley, 1985). The reticular neurons project to the thalamus and frontal, parietal, and occipital regions of the cortex. The cortex appears to be involved in the regulation of NREM sleep and the maintenance of wakefulness (Parkes, 1985) in that a feedback loop exists between the cortex and the reticular formation. The cortex can activate the reticular formation, which, in turn, activates the cortex, causing arousal. It is thought that thalamocortical projections produce cortical synchronization, or NREM sleep.

In the cat, stimulation of the midline thalamic nuclei produces sleep (Parkes, 1985). In man, lesions of the thalamus abolish sleep spindles, which may be responsible for the regulation of NREM sleep. Studies of fatal familial insomnia (FFI) have found that the anteroventral and dorsal medial (DM) thalamus are likely involved in the regulation of the sleep-wake cycle (Sforza et al., 1995). Postmortem neuropathological examination of patients with this disorder has found thalamic atrophy and astrogliosis in frontal regions. The EEG pattern of these patients consists of continuous wakefulness interrupted by episodes of REM. This pattern is somewhat similar to patients with FM, who experience "too much wakefulness" during sleep. Therefore, both the cortex and the thalamus appear be involved in the regulation of sleep, and thus, low rCBF in these areas in FM may reflect the sleep disorder that occurs in these patients.

Low rCBF in caudate nucleus

That the caudate nucleus is also implicated in FM is not surprising because this structure is thought to be involved in pain. For example, somatosensory neurons within the caudate nucleus and putamen of the rat have been found to detect the occurrence of noxious stimuli (Chudler, Sugiyama, & Dong, 1993). Application of a pinch stimulus to the receptive field of these nociceptive neurons results in a rapid increase or decrease in neuronal activity. The Bradley et al. (1994) study also found decreased rCBF in the caudate nucleus in FM and CPUE, both of which are conditions involving pain. Thus, low rCBF in the caudate nucleus of patients with FM may somehow reflect the chronic pain experienced by these patients.

Low growth hormone

Finally, low growth hormone in FM may also be an underlying cause of some of the symptoms of the disorder, particularly pain. As already mentioned, GH is mostly released during Stage 4 sleep, which is greatly reduced or disrupted among patients with FM. This may explain why GH levels are low. Growth hormone stimulates the synthesis of DNA, RNA, and proteins and is thus involved in muscle homeostasis (Bennett et al., 1992). Bennett et al. (1992) have hypothesized that patients with FM have a defect in normal repair processes of muscles after exertion due to inadequate levels of GH, resulting in increased pain.

Part 2: Models on Which to Base the Evaluation of Cognitive Functioning Among Patients with Fibromyalgia

It appears that the pathophysiological findings identified so far in FM are likely related to their symptoms of pain, poor sleep, and depression. The CNS areas and systems involved in pain, sleep, and mood, namely the cortex, thalamus, and caudate nucleus and the serotonergic neuronal network, are also involved in cognition. Thus, it is possible that FM could also involve deficits in cognitive functioning.

Other patient populations besides those with FM have been found to have low rCBF in cortical and subcortical structures. Examination of the performance of these patients on neuropsychological measures may help to provide a model on which to base the evaluation of cognitive functioning in FM. However, the studies to be presented next involve patients with actual lesions of subcortical structures. Caution will be necessary when inferring that the same pattern of cognitive deficits might occur in FM because no lesions have been found among patients with this disorder. In the following sections, examples of studies reporting on the cognitive effects of cortical, thalamic, and caudate lesions and of low levels of central serotonin will be briefly presented.

Effects of Thalamic Lesions on Cognition

Levasseur et al. (1992) measured cerebral metabolism using PET in seven patients with paramedian thalamic infarcts, who reportedly had damage to the dorsal medial and intralaminar nuclei of the thalamus. Diffuse cortical hypometabolism was found in all patients. Language impairment was found in three subjects, as measured by a word list generation task, a test of naming ability (Goodglass & Kaplan, 1983), and the Similarities subtest of the WAIS. Memory deficits were also evident in all patients, according to their performance on the Rey-Osterrieth Complex Figure Test and the Wechsler Memory Scale (Wechsler, 1974). Also, most of the patients displayed impaired executive functioning (Wisconsin Card Sorting Test; Grant & Berg, 1948) and attentional deficits (graphic alternating sequences; Luria, 1966).

Other studies have described the neuropsychological functioning of patients with lesions confined to the thalamus. For example, Puel et al. (1992) examined neuropsychological functioning and cerebral blood flow using SPECT among patients with small ischemic or hemorrhagic lesions of the left anterior, ventral anterior (VA), pulvinar, and VL nuclei of the thalamus. SPECT scans showed low rCBF in the left and right caudate nuclei, left thalamus, and temporal and occipital regions. Corresponding language deficits included marked loss of spontaneous language, anomia, and a comprehension and writing impairment.

Another study by Mennemeier, Fennell, Valenstein, and Heilman (1992) found neuropsychological deficits in a patient who had a nonhemorrhagic lesion of the left intralaminar nuclei and portions of the medial nuclei of the thalamus. The patient was administered measures of memory, language, and attention. In terms of language functioning, the patient performed below average on verbal fluency task, although her naming abilities were normal. Her memory performance was severely impaired as measured by the consonant trigrams task. Here, she performed normally during shorter delays, but became more impaired than normals as the delay time increased. It was suggested that the distraction component of this task significantly interfered with her ability to remember the three letters. She was also slow at acquiring verbal information on the California Verbal Learning Test (CVLT; Delis, Kramer, Kaplan, & Ober, 1987), although she was eventually able to learn and retain the information.

These studies suggest that cognitive deficits, involving language, memory, and attention, occur in patients with lesions of the thalamus. Language impairment involved word list generation, naming, and comprehension abilities. These patients were slow at acquiring verbal information, were impaired on a measure of visual memory, and displayed attentional deficits that appeared to interfere with memory functioning.

It has been suggested that low cortical blood flow or low cortical energy metabolism in cases of thalamic lesion may reflect deafferentiation of the cortex (Levasseur et al., 1992). For example, the intralaminar nuclei, which was affected in the Levasseur et al. 1992 study (in which diffuse cortical hypometabolism was found), project diffusely throughout most of the cortex (Crosson, 1992). The thalamus makes up part of several cortico-subcortical pathways. Alexander, DeLong, and Strick (1986) described cortico-striato-pallido-thalamo-cortical loops which involve projections from prerolandic cortex to the striatum, from the striatum to the globus pallidus and/or substantia nigra, from the latter two structures to the thalamus, and from the thalamus back to the prerolandic cortex. There are also positive feedback loops that exist between the thalamus and cortex (Penney & Young, 1983). Thus, because there are diffuse projections from the thalamus to the cortex, is possible that lesions of this structure could cause deafferentiation of the cortex.

Effects of Lesions of the Caudate Nucleus

Studies have also reported impaired neuropsychological functioning and low blood flow in the cortex of individuals with caudate nucleus lesions. Pozzilli, Passafiume, Bastianello, D'Antona, and Lenzi (1987) measured blood flow using SPECT in two patients with lesions of the caudate nucleus. One patient was emotionally flat and displayed inhibited spontaneous language. The second patient showed a verbal comprehension deficit on the Token Test (De Renzi & Vignolo, 1962), impaired performance on the Babcok short story (De Renzi, 1977), Learning of Verbal Paired Associates (De Renzi, 1977), and Digit Span and was impaired on a measure of verbal fluency. Thus, this study found deficits in verbal comprehension, verbal memory, verbal fluency, and attention in a patient with involvement of the caudate nucleus and the cortex. Because both of these structures are also involved in FM, similar cognitive impairment could be expected.

Effects of Low Central Serotonin on Cognition

In addition to low rCBF in the cortex, thalamus, and caudate nucleus, low central serotonin levels were also found among patients with FM. There is some evidence that cognitive deficits are associated with low levels of this neurotransmitter. The effect of low serotonin on cognition in normals, patients with major depression, and rats has been investigated. For example, Park et al. (1994) studied the effects of L-tryptophan depletion on human cognitive performance. Tryptophan is an amino acid that is essential for the synthesis of serotonin. The authors administered a low tryptophan amino acid drink to healthy subjects. This liquid reportedly decreased the supply of tryptophan to the brain by lowering plasma tryptophan levels and by restricting its entry into the brain through the competition from other amino acids for transport across the blood-brain barrier. It was reported that, in previous studies, this drink had been found to decrease central serotonergic activity in both rats (Fernstrom & Wurtman, 1971) and man (Young, Smith, Pihl, & Ervin, 1985). A placebo drink was given to half of the subjects.

Subjects were then administered several neuropsychological tests. On a computerized visuospatial paired associates task, the experimental group required a significantly greater number of trials to learn the associations and made significantly more errors than controls. On a computerized version of the Tower of London test, which measures planning abilities, the low tryptophan subjects were slower, but required the same number of moves as the controls. Thus, the experimental group showed longer thinking times on this task. A visual discrimination (attentional set shift) test based on the WCST was also given. The low tryptophan group required more trials to reach criterion and made more errors on this measure.

Blood tests showed that the low tryptophan drink had successfully lowered plasma total and free tryptophan in the experimental group, and it was assumed that central serotonergic synthesis was also lower. Thus, according to the results of this study, serotonin may play a part in learning, thinking speed, and the ability to shift set.

Nomura (1992) found similar results in a study in which serotonergic dysfunction was induced in rats by way of a low tryptophan diet. Here, low serotonin was found to impair performance on an operant discrimination learning task in which a rat had to learn to press a lever for food during periods of bright illumination of the cage. Therefore, these findings also suggest that serotonin may be involved in learning.

Studies of the performance of depressed individuals on neuropsychological measures also support the idea that low serotonin has an effect on cognition. Depression has been associated with low levels of serotonin in the brain, and cognitive deficits have been found among depressed patients in many studies. For example, Weckowicz, Tam, Mason, and Bay (1978) compared the performance on several psychomotor speed tests in depressed and nondepressed subjects. Also given were the Information and Comprehension subtests of the WAIS. Although there were no significant differences between depressed and nondepressed subjects on the intelligence tests, the depressed group was significantly slower on 6 of ten psychomotor measures.

The fact that intellectual functioning was preserved among patients with depression in this study is consistent with the reports of many other studies (Miller, 1975), although some have reported poorer Performance I.Q. as compared to Verbal I.Q, suggesting right hemisphere dysfunction (Flor-Henry & Grozelier, 1983) in these patients.

Slowed mental processing, attentional deficits, and impairment in short-term memory have also been reported in depressed patients. For example, Lemelin et al. (1996) evaluated the performance of 30 nonmedicated depressed individuals and 30 normal controls on two tests of attention. Patients had to meet the criteria for major depressive episode according to the DSM-III-R (Diagnostic and Statistical Manual of Mental Disorders; American Psychiatric Association, 1987). The first test, the Stroop Color-Word Test (Stroop, 1935), involves concentration and the ability to ignore distractions, according to Lezak (1995). Here, depressed subjects had longer reaction times and were more susceptible to interference by a distraction than controls. The second task was called the Visuo-Spatial Interference Test, which was a computer test developed by the examiners as a measure of the ability to attend selectively to a stimulus and to inhibit responses to a distracter. Reaction time was reportedly significantly slower among depressed as compared to control subjects on this test. This study suggests that depressed individuals have difficulty with selective attention and are more likely to be distracted by irrelevant stimuli.

Depression may also affect higher problem-solving ability. For example, Martin, Oren, and Boone (1991) administered the WCST to depressed, dysthymic, and control subjects. Diagnoses of major depression and dysthymia were made according to DSM-III-R criteria. Also given were the Verbal subtests of the Wechsler Adult Intelligence Scale--Revised (WAIS-R; Wechsler, 1981). The depressed and dysthymic group attained Verbal I.Q. scores that were in the average range. Performance on Digit Span was significantly affected by depression, suggesting that this population exhibits deficits in attention and immediate memory. On the WCST, depressive symptoms correlated with number of errors, perseverations, and failure to maintain a set on this measure. Thus, depression is apparently associated with deficits in executive functioning and immediate memory.

Depressed patients also appear to be impaired on tests of verbal learning. Wolfe, Granholm, Butters, Saunders, and Janowsky (1987) demonstrated that patients with major depression were slower to learn a list of words on the Rey Auditory Verbal Learning Test (RAVLT; Rey, 1964) and recalled fewer words over five trials than a group of normal controls. They were as able to retain the words they had learned, however, over a 20-minute delay. Thus, the depressed patients were slower than normals in learning verbal information and displayed poorer immediate recall. Therefore, depressed patients appear to have deficits in executive functioning, immediate verbal memory, verbal learning, attention, and psychomotor speed.

The above studies suggest that individuals with low levels of central serotonin display cognitive deficits, including impaired memory, attention, learning, and executive functions, such as problem solving and the ability to maintain a set, and exhibit slowed psychomotor speed. Results of studies involving depression provide only tentative proof this, however, because other neurotransmitters in addition to serotonin are involved in this condition that could account for the reported cognitive difficulties.

Patients with depression have been reported to have low rCBF in the cortex (Schwartz et al., 1994). Therefore, low central serotonin may be associated with hypoperfusion in the cortex. As already discussed, there are serotonergic projections throughout the brain, including the thalamus, striatum, and cortex. Thus, it is possible that low rCBF in the thalamus, caudate nucleus, and cortex of patients with FM could reflect decreased serotonergic input to these areas.

In summary, other populations with similar cortical and subcortical involvement have been found to have cognitive deficits involving naming, word list generation, verbal memory (specifically in terms of the rate of learning new information), visual memory, attention, and low psychomotor and mental processing speed. The attentional deficits appear to interfere with memory functioning. Thus, it will be important to use these findings as a model on which to base the evaluation of cognitive functioning in FM.

Part 3: A Review of the Literature on Cognitive Functioning in FM

Subjective clinical complaints among people with FM include difficulty "finding a word" at times during conversation, difficulty retrieving remotely-learned and newly learned information on demand, and difficulty concentrating, which, they claim, interferes with their ability to learn new material. Despite these complaints, only three studies have examined cognitive functioning in FM. Sletvold, Stiles, and Landro (1995) measured information processing capabilities in 25 patients with FM, who fit ACR criteria for the disorder, 22 patients with major depression, diagnosed according to DSM-III-R criteria, and 18 healthy controls, who were free of rheumatic or psychiatric illness. According to the authors, information processing involves speed of responding, attention, and working memory, which they defined as "the ability to combine moment-to-moment awareness and instant retrieval of archived information" (p. 137). To test information processing abilities, several neuropsychological measures were administered, including the Digit Symbol subtest (DST) of the WAIS, which the authors regarded as a test of psychomotor performance. Lezak (1995) suggests that this test measures motor persistence, response speed, sustained attention, and visuo-motor coordination. The Trail Making Test, was given as a test of speed and attention. The Paced Auditory Serial Addition Task (PASAT; Gronwall, 1977) was also included in the battery, which Lezak (1995) describes as being a test of information processing and attention. The authors used a modified version of this task in which digits were presented at only two rates of speed (every 2 and 4 seconds). A computerized test of reaction time and response inhibition was also given. In the reaction time task, subjects had to press a key with the hand that corresponded to the side of the monitor on which a stimulus was presented. In the inhibition task, subjects had to inhibit this response when a tone was presented simultaneously with the stimulus. The Block Design subtest of the WAIS was given as a test of visuoconstructive ability. The Similarities subtest was also included, which is sensitive to left hemisphere damage and is thought to indicate verbal conceptual and abstract thinking abilities (Lezak, 1995). As a measure of depression, the BDI was given to all subjects.

Both the FM and the major depressed group were depressed according to the BDI, whereas the control subjects were not. The major depressed group was significantly more depressed than both the FM and control groups, and the FM group was significantly more depressed than the controls. Scores on Similarities and Block Design were not significantly different among the three groups, although the depressed group scored significantly lower on Block Design than on Similarities. There were no significant differences between Similarities and Block Design scores in the FM or control group.

Overall group differences were reported on the Digit Symbol Test, PASAT 2.0 (seconds), PASAT 4.0, reaction time for the left hand (RTL), and inhibition of the left hand (Inhib-L). There were no significant differences in performance on any of the tests between the FM and depressed group, but significant differences were reported between these two groups and the controls. It is unclear what these differences were, however, because the authors stated that these groups performed significantly "slower" on the DST, PASAT, RTL, and Inhibit-L task than the control group, yet did not report any score that involved speed of responding for the DST and PASAT. The score used in the analysis was reportedly the number of correct responses on the DST and percent correct on the PASAT. However, the mean score reported for the FM group on the DST is 10.5, which is most likely a scaled score. If so, this score is in the average range, and may be significantly lower than that achieved by the normals used in this study (13.5), but it cannot be stated that the FM patients showed evidence of cognitive impairment on this measure because they actually scored in the normal range. The control group chosen for the study obtained an unusually high score for this subtest. Thus, it is erroneous to suggest that FM subjects are impaired on this measure.

The PASAT 2.0 score that was reported for the FM group was 51.1. This score appears to represents the percent correct on the measure, and thus, the FM group performed in the impaired range (test norms indicate that normals usually answer 80% of the items correctly). Although the FM group scored significantly different on the PASAT 4.0 than the controls, there are no normative scores for this measure, and thus it is not possible to firmly conclude that the FM patients were impaired. Thus, the mean score of the FM group indicates that they performed normally on the DST, but they showed deficits on the PASAT 2.0 and, possibly, the PASAT 4.0.

There was a trend towards slower performance by the FM and depressed groups than the controls on the Trail Making Test, but these scores were not significantly different. The authors did not point out, however, that the FM group's score on Trails B (98.4) was actually in the mildly impaired range according to the norms provided by Reitan (1985).

The score reported on the inhibition task was the subject's mean reaction time, but the authors did not denote the number of errors made on this task. Apparently, the FM and depressed group had difficulty in this task because their left-handed responses were slower as compared to normals. It is unclear, however, if this reflects motor slowing among these subjects or if the inhibition task was distracting and caused increased time to respond. Both groups performed more slowly than controls when using their left hands during a simple reaction time task. The handedness of the subjects was not reported, however, so it was not possible to tell if all of the subjects in the study were using their nondominant hand during the left-handed tasks. The right-handed score (264 seconds) for the normals was actually somewhat slower than the left-handed score (254 seconds) suggesting that some of these subjects may have been left-handed. Thus, it can only be suggested that depressed and FM subjects may display motor slowing on the simple reaction time test. The results of performance on these tests are somewhat inconclusive.

Because there was a substantial proportion of patients who apparently exhibited depression in the FM group, the authors chose to divide these subjects into one group with a lifetime history of depression and another without (based on the Structured Clinical Interview for DSM-III-R; Spitzer and Williams, 1984). The group without a lifetime history of depression was then found to be significantly less depressed than the group with a lifetime history, according to their BDI scores. The former group had an average score of 11 on the BDI, which indicates mild depression according to normative data obtained from nonpain subjects, whereas the latter group scored 14.8 on this measure, indicating more moderate depression using the same norms.

It is erroneous to assume, however, that the BDI scores obtained by the FM group were actually indicative of depression in these subjects. Several items on this measure have been found to reflect physical disease symptoms, and thus, may or may not reflect depression in the individual who endorses the item (Callahan, Kaplan, & Pincus, 1991; Peck, Smith, Ward, & Milano, 1989; Williams & Richardson, 1993). For example, the item that states "I can work about as well as before" could obviously be negatively endorsed by a chronic pain patient who is not depressed. Although Turner and Romano (1984) have suggested a cut-off score of 13 on the BDI for identifying depression in chronic pain subjects, Williams and Richardson (1993) suggest that raising the cut-off score does not solve the problem because such a high proportion of the questions are related to somatic functioning. These authors also believe that the DSM-III-R criteria for diagnosing depression may also overestimate the prevalence or severity of depression in chronic pain groups because this method also incorporates the same confounding of somatic and nonsomatic indicators. Thus, it is not possible to conclude that the subjects in this study were, in fact, depressed.

The group defined as being without a lifetime history of depression (N=14) was deemed the nondepressed FM group. This group, as compared to normal controls, had significantly worse scores on the PASAT 2.0. Although it was not discussed, the nondepressed FM subjects also performed in the mildly impaired range (102) on the Trail Making Test. Apparently, no analyses comparing the depressed versus nondepressed FM subjects were carried out. Based on comparisons between the nondepressed FM subjects and controls, the authors concluded that, when the effect of depression on test scores was factored out, patients with FM still showed deficits in information processing.

Thus, this study tentatively supports the notion that FM patients may display cognitive deficits, specifically in attention and information processing (which involves working memory). It is not possible to draw firm conclusions based on this report, however, because it was unclear what scores were used in the study. Some of the FM subjects appeared to be depressed, although the exact percentage is unclear because of confounding items on the measure used to test for depression (BDI). Also, no mention was made of whether or not the patients were medicated, and thus, the possible effect of medication on performance was not analyzed. The attentional deficits found among FM patients were apparently not related to depression. FM patients did not display lower Performance I.Q. as compared to Verbal I.Q. as did the depressed subjects, suggesting that FM patients may have a different pattern of cognitive deficits than the latter group.

Sletvold et al. (1995) published another paper two years later using the same group of FM, major depression, and healthy control subjects (Landro, Stiles, & Sletvold, 1997). The purpose of this paper was to describe memory functioning in FM. To do so, they administered Digit Span, the Randt Memory Test (Randt & Brown, as cited in Landro et al., 1997), a word fluency task (FAS), the Code Memory Test (Levander & Elithorn, as cited in Landro et al., 1997), and the Kimura Recurring Recognition Figures Test (Kimura, as cited in Landro et al., 1997). The Randt Memory Test includes a measure of general information, a list learning paradigm, an associative paired words task, a short story recall test, a picture recognition task, and a test of incidental learning. The Code Memory Test requires active retrieval of newly learned information after the subject performs an interfering cognitive activity. Kimura Recurring Recognition Figures requires the subject to identify previously viewed geometric figures from among 60 “new” and “old” designs. The authors deemed the word fluency task a measure of semantic memory. They also considered Digit Span to be a test of short-term memory and suggested that the rest of the memory battery was made up of long-term measures.

As described in Sletvold et al. (1995), the FM group was divided into depressed and nondepressed groups. However, in this study, analyses were conducted between these two groups. Although there were no differences found between the depressed and nondepressed FM groups on any of the above memory measures, the depressed FM group performed significantly worse than the healthy controls on the Randt Memory Test and the Code Memory Test. There were no significant differences between the nondepressed FM group and the healthy controls. None of the groups were impaired on Digit Span, The Kimura Figures, or Incidental Memory. Although, statistically, both the total FM group and the group with major depression scored significantly worse than the healthy controls on FAS, none of these groups were impaired on this test according to FAS norms (Spreen & Strauss, 1998).

The FM group had a significantly lower education level than both the healthy control and the major depression groups. In spite of this, education level was not covaried out during comparisons between the FM groups and the group with major depression. Therefore, the memory results reported were inherently confounded by educational differences between the groups. Thus, it was not possible to compare memory functioning in FM versus major depression. The group with major depression reportedly scored significantly worse than controls on all memory measures except Digit Span. Landro et al. (1997) concluded that, based on the above results, depressed FM subjects and those with major depression are impaired on measures of long-term memory, as measured by the Randt and the Code memory tests, but not short-term memory, measured by Digit Span. They suggested that memory impairment in FM only occurs if concomitant depression is present.

Correlations were carried out between pain intensity and fatigue and scores on the Randt and Code memory tests. Pain and fatigue were measured using a visual analog scale. No significant relationship was found between either of these variables and memory performance. Unfortunately, an overall score was reported for the Randt Memory Test, but no individual scores were sighted. Therefore, it was not possible to determine how subjects performed on the individual tasks. It would have been of interest to evaluate if the depressed FM group performed more poorly than controls on both verbal and nonverbal subtests of this measure. FM subjects performed normally on the Kimura Figures, a measure of visual recognition, but it is uncertain whether or not deficits were found on the picture recognition task of the Randt Memory Test. Also, it was impossible to determine if the FM group had more difficulty overall on recall versus recognition measures because no verbal recognition tasks were administered.

Another difficulty with this study was that no mention was made of whether or not the FM group was medicated. Thus, it was not possible to determine whether or not medication may have been responsible for the deficits found in the depressed FM group. The group with major depression, reportedly, was not medicated. Thus, it could be said for certain that medication was not responsible for the impaired functioning in that group.

In summary, it appears that depressed FM patients are impaired on tests of memory, but it is not certain if these deficits are for both verbal and visual information and if they involve both recognition and recall. It is also not possible to determine from this study, what, if any, effects medication may have had on cognitive performance among these subjects.

A third study (Kaplan et al., 1992) compared the performance of 20 patients with Lyme encephalopathy, 11 FM patients, and 11 nonpsychotically depressed patients on the CVLT, WMS, and Rey-Osterrieth Complex Figure Test (Osterrieth, 1944). The latter two groups acted as comparison subjects because, reportedly, depressed and FM subjects have similar symptoms to Lyme encephalopathy patients. No information was provided concerning how the patients with FM were diagnosed or from where they were recruited, nor were the criteria for a diagnosis of depression in the depressed subjects reported. Each subject's I.Q. was determined using the WAIS-R or the Shipley Hartford Institute of Living Scale (Zachary, 1986).

Depression was measured using the MMPI. Both the FM and the depressed groups had T-score elevations above 70 on the Depression scale, suggesting that both of these groups were significantly depressed.

No significant differences in I.Q. were found among the three groups, and they all scored within the average range. The only subtest of the WMS on which the FM showed some difficulty was Logical Memory (scaled score = 6.7). The FM group performed normally on the CVLT. Specifically, they scored within the normal range on Trial 5, Short Delay Free Recall, Long Delay Free Recall, and Recognition.

On the Rey-Osterrieth, it appears that the reported score is a percentile (35.9 for immediate recall and 35.3 for delayed recall), although this also was not stated. On this measure, the variance was large (a standard deviation of 12.2 for immediate recall and 11.6 for delayed recall), suggesting that some patients with FM were impaired on this measure.

There were no apparent differences between the FM and depressed subjects on any of the measures. Depressed subjects, however, had a significantly higher level of education than did the FM subjects. Thus, it is possible that the FM subjects may have performed better than the depressed group if this had been taken into account.

Thus, some FM patients appeared to display problems with immediate verbal memory (Logical Memory subtest), and possibly, with immediate and delayed visual memory (Rey-Osterrieth) in this study. However, in spite of being depressed, the FM subjects performed normally on the CVLT. This finding is inconsistent with the results of the Landro et al. (1997) study, which reported that depressed FM subjects have memory impairment. However, it is difficult to draw any conclusions based on this study because only a small number of FM patients were tested, the criteria by which they were diagnosed is unknown, the reported scores were unclear, education differences were not accounted for, and it was unknown if the FM group was medicated.

Thus, the Sletvold et al. (1995), Landro et al. (1997), and the Kaplan et al. (1992) studies suggested that FM patients may display mild cognitive deficits, although they appeared to perform in the average range on intelligence tests. Impaired performance that could not be explained by depression was found on tests of attention (PASAT and TMT) among FM subjects.

Depressed FM patients appeared to perform significantly worse on memory tests as compared to healthy controls in Landro et al. (1997). However, it was unclear in this study if these deficits involved both visual and verbal memory and/or both recall and recognition of material. It was not possible to tell from any of these studies cognitive deficits were related to use of medication, or if performance varied according to severity of illness.

There are inconsistencies among the results of the above studies, possibly due to methodological problems, such as using poorly defined groups, failing to account for differences in education level, and medication status. Thus, it is still unclear if FM patients exhibit cognitive deficits.

Part 4 - Summary and General Hypotheses

Summary

Fibromyalgia is a complex syndrome that involves symptoms of pain, fatigue, depression, anxiety, and disrupted sleep. It is reportedly associated with low central serotonin levels, low serum growth hormone levels, altered immune system functioning, and low rCBF in the cortex, thalamus, and caudate nucleus. Studies have shown that individuals with similar types of pathophysiology display cognitive deficits in the areas of language, memory, attention, and executive functions. Thus, it is possible that FM patients have similar cognitive deficits. Only three studies, none of which were methodologically sound, have examined this possibility. These studies suggested that FM patients were mildly impaired on tests of attention and verbal and visual memory, although they performed normally on intelligence tests. Depression may have been related to deficits in memory functioning. However, attentional difficulties appeared to occur independently of depression, and thus, depression may have caused some, but not all, of the reported cognitive impairment associated with the syndrome.

General Hypotheses

The present study attempted to describe cognitive functioning in FM by examining the performance of these patients on several neuropsychological measures and by comparing their performance to that of normal controls. Because subjective clinical complaints among people with FM include impaired language, memory, and attentional abilities, and because FM involves dysfunction in regions of the brain that are associated with impairment of these cognitive abilities, all three of these domains abilities were examined. This was the first study to examine naming abilities in FM.

The current study attempted to replicate the findings of previous studies using a greater number of subjects. In addition, the effects of depression, anxiety, pain level, fatigue, and severity of illness on cognitive functioning were examined. Finally, the performance of medicated patients was compared to unmedicated patients to see if cognitive abilities were affected by medication.

It was hypothesized that patients with FM might show evidence of mild verbal and visual memory and attention deficits, as was found in the previous studies on cognition in FM. Based on subjective complaints, it was also expected that word retrieval problems would be found. Performance on cognitive measures were expected to vary as a function of depression, anxiety, pain level, and/or severity of illness in FM, a possibility that had not yet been extensively investigated in previous studies. As discussed above, depression has been associated with cognitive deficits across many domains, and thus, a negative correlation between level of depression and cognitive scores was expected. Anxiety has been found to interfere with working memory (Darke, 1988) and sustained attention (Kopp, 1989), and thus a negative association between anxiety and scores on these types of measures was expected. Pain has been found to produce attentional deficits (Eccleston, 1995), and thus a negative correlation between attentional performance and level of pain was expected. Also, it was expected that patients who were more severely affected by the illness would perform more poorly on cognitive measures.

Medication can affect performance on cognitive measures. It was thought that patients who were medicated with an antidepressant might do better than those who were untreated, although some antidepressants that have a sedative effect produce impairment on measures of attention, memory, and learning (Amado-Boccara, Gougoulis, Littre, Galinowski, and Loo, 1995). Finally, FM subjects were likely to perform in the normal range on intellectual meaures, as was found in the previous studies. More specific hypotheses related to each of the measures used in the current study are listed in at the end of the Method section, following a description of each of the measures employed.

CHAPTER 2
METHOD

Subjects

Twenty-four female subjects with FM, diagnosed according to ACR criteria, were recruited from among FM patients at the Department of Rheumatology at Shands Hospital (N=17), Shands Hospital employees (N=3), University of Florida students (N=1), University of Florida faculty (N=1), and an FM support group in Gainesville (N=2). FM subjects were between the ages of 21 and 60 and were free of concomitant rheumatic or other medical illness, chronic pain (due to a condition other than FM), psychiatric diagnosis (other than depression or anxiety disorder), previous head injury with loss of consciousness, and previous or current alcohol or drug abuse. Subjects who were not rheumatology patients at Shands Hospital at the time of recruitment were screened by a Shands rheumatologist to ensure that the above criteria were met prior to being included in the study. Data from one subject was thrown out because she became too anxious to complete testing, and thus, the battery was terminated prematurely. Another subject was subsequently recruited to take her place in the study.

Twenty-four healthy female subjects in the same age range were used as controls. These subjects were recruited from among Shands Hospital personnel and University of Florida and Santa Fe Community College students by means of advertisements placed throughout the hospital and campuses. Healthy controls were also recruited from among citizens in the community through an advertisement placed in the local newspaper. Healthy controls were free of rheumatic or other medical illness, chronic pain, previous or current psychiatric diagnosis, previous head injury with loss of consciousness, and previous or current drug or alcohol abuse.

Procedure

The current study was a descriptive study in which FM and control subjects were administered an identical battery of tests, all of which were given during one testing session. Subjects were tested in a quiet room at Shands Hospital. All of the FM subjects and the first 8 control subjects were paid $ 8.00 for their participation in the study, plus $ 2.00 for parking reimbursement. When it became evident that an adequate number of control subjects could not be recruited at this level of pay, the pay was increased to $20.00, plus reimbursement for parking. Thus, the remaining 16 control subjects were paid an additional $12 for their participation.

Screening Procedures

To ensure that FM subjects met the exclusionary criteria described above, the examiner consulted with the subject's physician, reviewed the subject's medical record, and interviewed the subject. The examiner met with the subject at her scheduled rheumatology appointment to inquire as to her interest in participating in the study. If the subject was interested, dolorimeter testing, as described below, was carried out at this time to ensure that the subject met ACR criteria for FM. Next, the FM screening form was administered (see Appendix A). Control subjects were screened for age, education level, and the above exclusionary criteria by telephone (see Appendix B).

All subjects were screened for depression using DSM-IV (American Psychiatric Association, 1994) criteria with a DSM-IV checklist (see Appendix C). This excluded any cases of clinical depression among the normal controls and allowed for documentation of any cases of clinical depression in the FM subjects. Depression screening occurred at the time of testing for FM subjects. Controls were asked these questions during their telephone screening. All subjects were screened for previous or current alcoholism using the "CAGE" examination (Mayfield, McLeod, & Hall, 1974).

FM Subjects' Characteristics Questionnaire

A questionnaire was administered to FM subjects (see Appendix D) at the end of the testing session that asked them to list all of their medications, including dosages and length of time on each medication. It also asked when they were first diagnosed with the illness. Many times, patients with FM are ill for several years prior to being diagnosed with the condition, and thus, length of time since diagnosis is not always an accurate indication of the true length of illness. Thus, the questionnaire also inquired as to how long they had been experiencing the symptoms of FM.

Severity of Illness Measures

Three measures were administered to assess the level of physical symptomatology in the patients with FM. They were also given to the controls to provide age- and education-matched healthy normative data for the FM group. These measures acted as independent measures in the study. Three scores of severity of illness were obtained, as described in the next section.

Dolorimeter Testing

A dolorimeter score was determined for each subject. A dolorimeter is an instrument that is used for quantitative assessment of tenderness at tender points among patients with FM and other pain conditions. It was used to calculate the mean amount of pressure required to produce pain in subjects across all 18 tender points, as has been done in several other studies (i.e., Russell et al., 1992). The examiner was instructed in the use of the dolorimeter by the rheumatologist (Dr. Schiffenbauer) involved in the study. The instrument was applied to each tender point by the examiner and was advanced at a rate of 1 kg per second. The subject was instructed to "tell me when this becomes painful" as in Wolfe et al. (1990). The mean score to produce pain across all 18 tender points was then calculated in kg.

Dolorimeter testing was done during the initial interview with each FM patient (at their rheumatology appointment) to ensure that they meet ACR criteria for FM prior to being invited to participate in the study. At this time, the dolorimeter was applied to each tender point at a pressure of 4 kg to determine if pain was present at 11 of 18 tender points. At the time of testing, dolorimeter testing was repeated ensure that they still met ACR criteria. Here, testing was carried out using the Russell et al. (1992) method as described above so that a mean score for the amount of pressure needed to produce pain across all 18 points could be calculated. It was possible to ensure that subjects still meet ACR criteria at the time of testing from this method.

Dolorimeter testing was also done with the control subjects at the time of testing. The dolorimeter testing was administered to ensure that control subjects did not meet ACR criteria for FM. They had also been screened for chronic pain over the telephone. The mean maximum pressure required to produce pain across all 18 points was calculated for each control subject. This dolorimeter score allowed for the analysis of the relationship between level of pain and cognitive functioning among FM subjects.

Short Form--36 Health Survey (SF-36)

The second measure of illness severity, the Short Form--36 Health Survey (SF-36; Ware, 1993) involved an assessment of the level of symptomatology experienced by the subject over the four weeks prior to the day of testing and was referred to as the SF-36 four-week score. It allowed for an estimate of overall severity of illness for the FM subjects. The SF-36 is a measure of an individual's health functioning and quality of life. It was developed as part of a large medical outcomes study, involving more that 10,000 subjects, to allow for evaluation of the quality of health care and the comparison of patients with chronic health problems to the general population (Ware, 1993). A description of the SF-36 scales is as follows:

1) Physical Functioning scale (10 items)--examines the extent that health difficulties interfere with daily activities such as self-care, walking, climbing stairs, cleaning, and the ability to engage in various moderate activities (i.e., lifting a table) and more vigorous ones (i.e., running).
2) Role-Physical (4 items)--inquires about problems with work or other daily activities as a result of physical health problems.

3) Bodily Pain scale (2 items)--measures the intensity of pain and the extent to which pain interferes with the ability to work.

4) General Health (5 items)--examines individual's perceptions about own health status.

5) Vitality scale (4 items)--determines amount of time the patient feels energetic versus fatigued.

6) Social Functioning (2 items)--examines the extent to which physical health problems interfere with social functioning.

7) Role-Emotional (3 items)--determines if emotional difficulties interfere with work or daily activities.

8) Mental Health (5 items)--inquires about feelings of nervousness and depression.

The items and scales are scored such that a higher score indicates better health. The SF-36 has been extensively normed, yielding norms for a representative sample (N=2,474) of the general United States population, ages 18 to 94 (Ware, 1993). These norms are presented separately for males and females by seven age groups for each of the 8 scales.

The SF-36 was administered and scored according to the directions in the SF-36 manual (Ware, 1993). Subjects were instructed to answer the questions in terms of how they had been feeling during the last four weeks. Transformed, scaled scores were computed to allow for the comparison of the subjects' 8 scale scores to the norms for the general population, and to compare the FM subjects' scores with the controls' scores. Medical norms are also provided for this measure but were not used because there were no conditions similar to FM represented in the sample from which these norms were developed.

The mean of the transformed scores from the first 6 scales yielded a score describing the subject's overall level of physical functioning, and was called the SF-36 four-week score. The last two scales were not included in this score because they focus on mental rather than physical functioning.

Although there are only a few items in each scale of the SF-36, the internal reliabilities of the scales are acceptable. For example, Brazier et al. (1992) reported high internal consistency, using Cronbach's coefficient alpha, for the Physical Functioning scale (.93), the Bodily Pain scale (.85), and the Vitality scale (.96). Concurrent validity of the SF-36 has also been documented. For example, the correlation of the SF-36 with the Physical Functioning Scale of the Sickness Impact Profile (Bergner, Bobbitt, Carter, and Gilson, 1981) was found to be -.78 (Weinberger et al., 1991). This correlation coefficient is negative because the scales run in opposite directions. Brazier et al. (1992) reported a correlation of -.68 between scores on the Vitality scale of the SF-36 and the Energy scale of the Nottingham Health Profile (Hunt, McKenna, McEwen, Williams, & Papp, 1981). Thus, the SF-36 appears to be a reliable and valid measure.

Visual Analogue Scale (VAS)

Visual Analog Scale (VAS) items were also administered to measure level of fatigue, pain, and malaise on the day of testing. Symptoms in FM vary from day to day and can be affected by factors such as starting to take a new medication or experiencing a recent stressful event. Thus, for the purpose of analyzing the possible relationship between severity of illness and cognitive ability, it seemed appropriate to include a measure that determined severity of illness symptoms at the exact time of testing. Thus, this score was also used to determine if a significant correlation existed between cognitive functioning and severity of illness.

The VAS questions were completed by subjects at the beginning of the testing session. Visual Analogue Scales have been used in several other studies on FM (i.e., Russell et al., 1991; Wolfe et al., 1995). The scale was 15 cm long, ranging from "None" to "The Most Intense Pain (or Fatigue, or Malaise) Imaginable" (Price, McGrath, Rafii, & Buckingham, 1983; Price, 1988). Visual Analogue Scales have been determined to be a valid method of measuring chronic pain (Price et al., 1983). Subjects were asked to rate their level of symptoms using the scale (see Appendix E). The mean of the scores on all three scales was calculated to obtain a severity of illness score at the time of testing, and thus, was called the VAS time-of-testing score.

Because dolorimeter testing itself could have slightly increased pain levels among subjects (as would have manual palpation of tender points), the Visual Analogue Scales were administered following this procedure so that this subjective measure of pain at the time of testing reflected the actual level of pain the subject was experiencing when testing began.

Thus, each subject had three severity of illness scores, including a dolorimeter score, four-week SF-36 score, and a time-of-testing VAS score.

Mood Measure

Profile of Mood States (POMS)

A measure of depression and anxiety was given to all subjects. This measure allowed for the determination of whether or not a correlation existed between these symptoms and scores on the cognitive measures. As already discussed, measures of depression commonly administered to FM patients contain confounding items involving physical symptoms that make interpretation of the scores difficult. Because of this, the present study used the Profile of Mood States (POMS; McNair, Lorr, and Droppleman, 1992) to measure depression and anxiety. The POMS was developed factor-analytically as a means to evaluate mood or affective states following various interventions, such as treatment with psychotherapy or drugs. It is a 65 item subjective measure of six mood or affective states: Tension-Anxiety; Depression-Dejection; Anger-Hostility; Vigor-Activity; Fatigue-Inertia; and Confusion-Bewilderment. Each item consists of an adjective that is responded to on a 5-point Likert rating scale (Likert, 1932), ranging from 0 = "Not at all" to 4 = "Extremely," designed to indicate the extent to which a particular adjective (i.e., "sad") describes the subject's mood. The subject is asked to rate how the adjective describes her feelings over the last week. Subjects completed the entire measure, to ensure a valid administration of the test, but only their scores on the Depression-Dejection (D) and Tension-Anxiety (T) scales were used in the analyses. Thus, this measure yielded two scores in the present study, a depression and an anxiety score, and acted as an independent measure in the study.

The D scale of the POMS contains no items related to physical complaints, yet it correlated well with the BDI ($r = .61$) in a sample composed of 287 solvent exposed workers

(McNair et al., 1992). Thus, although it contains no physical items, the POMS appears to be a valid measure of depression. The T scale correlated well (r = .80) with another measure of anxiety, the Manifest Anxiety Scale (Taylor, 1953), among 200 medical outpatients (McNair et al., 1992), suggesting it is also a valid measure of anxiety. Correlations between the D scale and the Depression scale of the MMPI-2, and the T scale and Psychasthenia scale of the MMPI-2, were also very high (.65 and .63, respectively; McNair et al., 1992). Good test-retest reliability was found by the test developers, using product moment correlations, for both the D scale (.74) and the T scale (.70). Thus, the POMS appears to be a reliable and valid measure of depression and anxiety.

Multiple studies have been carried out using the POMS that have yielded norms for male and female normal college students, medical outpatients, and psychiatric outpatients (McNair et al., 1992). FM subjects' scores were compared to both the scores of the normal subjects in the present study and the medical outpatient norms provided in the manual for 1,005 female medical outpatients. The long form of the POMS was administered because the norms were established using this form.

Neuropsychological Measures

The neuropsychological measures that were used in the present study will be described next (see Table 1). These acted as dependent measures, and included tests of language, attention, and memory. Intellectual screening was also done.

Language Measures

Boston Naming Test (BNT)

No studies of cognitive functioning in FM have measured naming in these patients. As already discussed, patients with FM report having difficulty "finding words". This type of difficulty may represent a word retrieval problem. To assess whether or not word retrieval problems exist among patients with FM, the Boston Naming Test (BNT; Kaplan, Goodglass, and Weintraub, 1983) was administered. This test is composed of 60 ink drawings of items ranging from ones that represent high frequency words to those that are less common.

Table 1

Neuropsychological Measures

Language
Boston Naming Test (BNT)
Controlled Oral Word Association (COWA) - letter "c"
Category Naming - animals

Attention
Paced Auditory Serial Addition Task (PASAT)
Auditory Consonant Trigrams (ACT)

Memory
California Verbal Learning Test (CVLT)
Rey Osterrieth (CFT) - (copy, immediate, and delayed)
Information Subtest
WAIS-R as a Neuropsychological Instrument (WAIS-RNI) - Information Subtest

Intelligence Screening
Comprehension Subtest
Block Design Subtest

Subjects are instructed to name each picture. This test is commonly used to elicit naming problems in aphasic patients (Lezak, 1995). Although FM patients are not aphasic, they seem to have difficulty with retrieving words that are in long-term storage. Goodglass and Kaplan (1983) suggest that the BNT is particularly useful for detecting mild word retrieval problems. Langfitt and Rausch (1996) used the BNT to test epilepsy patients who underwent anterotemporal lobectomy. The authors described the patients as having ". . . difficulty finding words in conversation. They frequently described having a word 'on the tip of their tongue,' but were unable to speak it" (p. 72). The authors labeled this problem a word-finding deficit. These patients scored significantly below published norms for the test. Fifty-five percent of the patients benefited from a phonemic cue, suggesting that the word was in long-term storage, but the patient was having difficulty accessing it. They also displayed circumlocution during attempts to correctly name the item. Thus, the BNT was sensitive to word-retrieval problems that were similar to the language complaints of those with FM.

The BNT was administered and scored according to the directions in Goodglass and Kaplan (1983) and Spreen and Strauss (1998). A total naming score was calculated to determine if actual naming deficits are present. Also, the number of correct responses following phonemic cue was calculated, and this number was divided by the number of phonemic cues that were required (the number of items that were originally missed by the subject). This yielded a score of the proportion of correct responses following phonemic cue. This score represented the number of times a subject experienced a word-retrieval problem because it reflected instances where she had the name of the item stored in memory but had difficulty retrieving it until the phonemic cue aided in its retrieval.

Multiple studies have demonstrated that the BNT has excellent internal reliability. For example, Huff et al. (1986) divided the original version of the test into two parallel forms and found a correlation between the two of .97 for a group of Alzheimer patients and .84 for a group of patients referred for neuropsychological evaluation. The BNT was found to load highly on a word knowledge factor in a study by Halperin, Healy, Zeitschick, Ludman, and Weinstein (1989), demonstrating the construct validity of the test. Education level has been found to affect performance on the BNT (Lezak, 1995), but the present study used education-matched control subjects to address this problem. Scores in the present study were also compared with the norms presented in Goodglass and Kaplan (1983), which were derived from the data of 84 normal adults, ages 18-59.

Word list generation measures

Two measures of word list generation were also administered because deficits in this area have been found among patients with thalamic involvement (Mennemeier et al., 1992). It was also given to determine if the previous report of normal FAS performance in subjects with FM (Landro et al., 1997) would be found in the current study. From the Controlled Oral Word Association Test (COWA; Benton & Hamsher, 1989), subjects were asked to generate a list of words beginning with the letter "c." This test was administered and scored according to the instructions in the manual (Benton & Hamsher, 1989), with the exception that only one letter was administered to reduce the experimental burden on the subjects. Test-retest reliability for this test has been found to be .88 in adults (desRosiers & Kavanagh, 1987).

Subjects were also asked to do a category (animals) naming task, which was administered and scored according to Spreen and Strauss (1998). Norms for this test are available in Goodglass and Kaplan (1983).

It was important to assess both animal and letter list generation because some populations have been found to have normal performance on one but not the other of these tasks. For example, patients with Alzheimer's disease (AD) can display impaired animal fluency but not letter fluency (Butters, Granholm, Salmon, & Grant, 1987), especially in earlier stages of the disease.

Attention Measures

Paced Auditory Serial Addition Task (PASAT)

Attention was assessed with the PASAT, which is a serial addition task that is administered with an audio tape. The subject is required to continuously add the last two numbers that have been presented and to state that sum aloud. Fifty numbers are presented in a series, and there are four series that are presented at four different rates of speed: one number every 2.4, 2.0, 1.6, and 1.2 seconds. According to Gronwall and Wrightson (1981), this task is a measure of sustained attention. Spreen and Strauss (1998) suggest that this is a complex mental tracking test that assesses rate of information processing. This measure was given as an attempt to replicate the earlier finding that FM subjects were impaired on one trial of this test. However, the entire measure was administered so that any difficulties with sustained attention could be described in more detail.

The PASAT has excellent split-half reliability (.96; Egan, 1988), which indicates that it has high internal consistency. Construct validity has been demonstrated in a factor analytic study by Larrabee and Curtiss (1995) in which the PASAT defined an attention/information processing factor. Performance on this measure varies according to education level (Spreen & Strauss, 1991). Gronwall and Wrightson (1974) have found the PASAT to be a sensitive measure of deficit among patients with mild head injury, and thus, it may be likely to validate the mild attentional complaints of people with FM.

The score on this measure was the percent correct responses for each of the 4 increasingly faster rates of presentation. A total number correct score was also calculated. Norms in Spreen and Strauss (1998) were used for this test.

Auditory Consonant Trigrams (ACT)

The Brown-Peterson technique (Peterson & Peterson, 1959), which is also called Auditory Consonant Trigrams (ACT), was also administered as a test of attention. This is a test of short-term retention that provides an opportunity to assess the effect of distraction on memory performance. Because it prevents rehearsal of material, it also measures the strength of an original memory trace (Lezak, 1995). The measure was administered according to the directions in Spreen and Strauss (1998). This task requires that the subject, upon hearing 3 consonants (such as "QLZ"), count backwards from a given number by 3's until told to stop counting, at which time they are to repeat the 3 letters. The letters need not be repeated in the same order in which they were administered in order to receive a correct score. Time required to count varies from 3 to 18 seconds.

Normal subjects display progressively poorer recall on the ACT as the delay between stimulus presentation and recall increases, suggesting that counting has a distraction effect (Lezak, 1995). Stuss et al. (1985) have found the ACT to be sensitive to detecting subtle neuropsychological deficits in patients with good recovery following closed head injury, suggesting that it may be sensitive to the mild attentional and memory deficits that patients with FM claim to have. Because this test required the subject to attend sufficiently to the original stimulus in order to develop a memory trace that was strong enough to remember, in spite of the distraction of counting and the prevention of rehearsal, it provided the opportunity to assess FM patients' complaints that attentional problems interfere with their ability to remember information.

Norms derived from Stuss, Stethem, and Pelchat (1988) based on the performance of normal controls were used. The scores were the percent of letters remembered for each of the four delay conditions (0, 3, 9, and 18 seconds). A total number correct score was also calculated.

Performance on the ACT test has been found to correlate with hippocampal metabolism in subjects ages 20 to 68 (Eustache et al., 1995). The hippocampus is a structure known to be involved in memory, suggesting that this measure is a valid measure of memory performance. This test has also been found to discriminate patients with multiple sclerosis, who are known to have impaired memory (Lezak, 1995), from normal controls (Grigsby, Ayarbe, Kravcisin, & Busenbark, 1994). The ACT has been found to correlate moderately with the PASAT (Spreen & Strauss, 1998), suggesting it is also a valid measure of attention. Performance on the ACT does not appear to be affected by age or education level (Spreen & Strauss, 1998).

Memory Measures

Information subtest

The Information subtest of the WAIS-R tests general knowledge normally available to persons growing up in the United States and can be considered to be a measure of remote memory (Lezak, 1995). This subtest was given to measure FM patients' complaints of difficulty retrieving remotely learned information. The test was administered and scored according to directions in the WAIS-R manual (Wechsler, 1981), with the exception that the discontinue rule was not followed. The reason for this will be explained in the next section. Scaled scores were used, which were derived from the age appropriate norms provided in the manual. The score was computed from the number of correct responses prior to incorrectly responding to 5 questions in a row (i.e., as if the discontinue rule had been followed).

This subtest has been found to have good test-retest reliability, with reliability coefficients ranging from .76 to .84 across various age groups (Goldstein & Watson, 1989). The concurrent validity of the WAIS battery as a whole was demonstrated by a correlation of .85 between the WAIS Full Scale I.Q. and the Stanford-Binet IQ (Wechsler, 1981).

WAIS-R as a Neuropsychological Instrument (WAIS-RNI)--Information subtest

The WAIS-RNI (Kaplan, Fein, Morris, & Delis, 1991) is an instrument that involves the administration and scoring of the WAIS-R in a manner designed to clarify errors made on the WAIS-R. It allows for an understanding of the processes that contribute to the performance of the subject. It provides multiple choice answers for the Information subtest of the WAIS-R and is given following administration of this subtest. After the subject completes the standard subtest, the multiple-choice responses to the questions that were missed are presented in a recognition format so that the subject can attempt to choose the correct answer. The multiple-choice format of this subtest was designed for patients who have retrieval problems. It allows for the measurement of their true level of knowledge not apparent in their responses to items presented in a free-response format.

The score for this test was calculated by dividing the number of correct responses following prompting with the recognition choices divided by the total number of questions missed on the Information subtest, yielding a score representing the proportion of times the subject benefited by cueing from the WAIS-R recognition format. This score allowed for the determination of whether or not FM patients benefitted from a multiple-choice format more than the controls, thus indicating whether or not this population appeared to display retrieval deficits.

California Verbal Learning Test

The California Verbal Learning Test (CVLT; Delis et al., 1987) is a verbal memory measure which involves a list of 16 shopping items (List A) that are read to the subjects five times, and the subject is required to freely recall all of the items after each presentation. The items can be grouped into four semantically related categories (tools, fruit, clothing, and spices/ herbs). After the learning trials, a second interference list of 16 items (List B) is presented and subsequently recalled by the subject. Free- and cued- recall trials of the original items are then administered immediately and again 20 minutes after the interference list. Finally, a “yes-no” recognition trial is given.

The criterion validity of the CVLT has been established in that it has been found to correlate very highly with another measure of memory, the WMS-R (Delis, Cullum, Butters, Cairns, & Prifitera, 1988). The CVLT has been found to be sensitive to memory deficits in head injury (Crosson, Novack, Trenerry, & Craig, 1988). Split-half reliability correlation coefficients of .77 to .86 have been reported for this measure (Delis, Kramer, Fridlund, & Kaplan, 1990). Thus, the CVLT appears to be a valid and reliable measure of memory functioning.

Performance on the CVLT is affected by age and education (Lezak, 1995), and thus, FM subjects’ scores on this measure were compared to age- and education-matched controls. Several scores from the CVLT were used to examine memory performance. The total-number correct on Trial 1 was used to evaluate immediate memory in FM (Delis et al., 1987). The total number correct on Trials 1-5 allowed for evaluation of learning as compared to controls. The number of items recalled on Trial 1, List A versus List B demonstrated any differential effects of proactive interference in the groups. Proactive interference is defined in Delis et al. (1987) as “the decremental effect of prior learning on the retention of subsequently learned material” (p.21). To examine possible effects of retroactive interference, defined in Delis et al. (1987) as “the decremental effect of subsequent learning on the retention of previously learned material” (p. 23), performance on the short delay free recall (SDFR) trial was analyzed. Here, the number of items recalled on the SDFR trial was divided by the number of correct responses on the subject’s best learning trial, generating a percent recall score for the SDFR trial. This score equated the subjects according to the number of items they had recalled initially (Crosson et al., 1993). Comparison of this score between the groups demonstrated any differential effects of retroactive interference between the FM and control groups. The semantic cluster ratio (calculated from the learning trials) was then used to examine the degree to which subjects used the active strategy of reorganizing words into categories for recall rather than employing the less effective strategy of serial clustering, or recalling items in the order they were presented (Delis et al., 1987).

To examine FM subjects' complaints of difficulties with recall, the percentage of items recalled on long delay free recall (LDRF) as compared to the number of items recalled initially by the subject was examined. To compare the groups on number of items recalled with cueing during both the short and the long delayed recall trials, the percentage of items recalled during long delay cued recall (LDCR) and short delay cued recall (SDCR) trials were calculated as described for free recall trials. Also, the percent of intrusions on the SDCR trials was calculated in this manner. This score was the only score found to discriminate between normals and head injured patients among all short delay scores (Crosson et al., 1993). Finally, recognition abilities were analyzed by comparing the discriminability index between the groups. This score is considered to be the single best measure of overall recognition performance and takes into account both the number of items correctly recognized and the number of false positives generated by the subject (Delis et al., 1987). An analysis of recognition ability as compared to recall ability demonstrated whether or not FM subjects appeared to have difficulty with retrieval of information.

Complex Figure Test (CFT)

Visual memory was assessed using the Rey-Osterrieth Complex Figure Test (CFT), which is a test that was designed by Rey (1964) as a measure of perceptual organization and visual memory. This test was chosen as an attempt to replicate previous findings using a larger sample size. The CFT was administered and scored according to the instructions in the Denman (1984) manual. It consists of a complex figure that the subject is first instructed to copy. Upon completion of the copy trial, the figure is removed and the subject is immediately instructed to reproduce the figure from memory. Following a 40 -minute delay, the subject is again asked to reproduce the figure from memory.

The Denman (1984) system yields age-appropriate scaled score equivalents of raw scores for the copy and the immediate and delayed reproductions. The copy of the figure will be scored to ensure that the subject has no perceptual or constructional difficulties. Then, if deficits are found on the reproductions, they will be attributed to memory impairment.

Performance on the CFT is significantly affected by age (Lezak, 1995). High interscorer reliability has been reported with this measure, with inter-rater reliability coefficients ranging from .85 to .97 (Tupler, Welsh, Asare-Aboagye, & Dawson, 1995). The CFT appears to be a valid measure of visual memory in that it has been found to successfully discriminate visual memory abilities in younger (ages 20-59) versus older (ages 60-80) subjects (Janowsky & Thomas-Thrapp, 1993; Tombaugh, Faulkner, & Hubley, 1992). Older subjects are known to perform more poorly on visual memory tasks than younger subjects (Lezak, 1995).

Intellectual Screening

Comprehension subtest

Two subtests of the WAIS-R were administered to subjects to screen them for intellectual functioning. The entire WAIS-R was not be given in order to reduce the experimental burden on the subjects. As an estimate of Verbal I.Q., the Comprehension subtest will be administered. This subtest is highly correlated with WAIS-R Verbal I.Q. (.76) across all age groups. Although the Vocabulary subtest is more highly correlated with Verbal I.Q., it takes twice as long to administer. Thus, the Comprehension subtest was used instead to decrease the experimental burden on the subjects. Also, this test relies less on recall of previously learned information than does the Vocabulary subtest. Thus, it may yield a better estimation of Verbal intelligence than the Vocabulary subtest in FM patients because this population has complaints of difficulty retrieving known information.

The Comprehension subtest evaluates the subject's practical reasoning ability, common sense judgment, and abstract thinking (Lezak, 1995). It was administered and scored according to the directions in the manual (Wechsler, 1981). Scaled scores were derived from the age appropriate norms provided in the manual. The reliability coefficients reported for this subtest range from .77 to .90, which indicate high internal reliability (Wechsler, 1981).

Block Design subtest

The Block Design subtest of the WAIS-R was administered to provide an estimate of Performance I.Q., as this test has the highest correlation (.70) with Performance I.Q. among all Performance subtests across all age groups. This is a timed construction test that measures visuospatial organizational abilities (Lezak, 1995). Reliability coefficients ranging from .83 to .89 are reported in the manual for this test across all age groups (Wechsler, 1981). The test was administered and scored according to the manual. Here again, a scaled score were derived from age appropriate norms provided in the manual.

Order of Administration of Tests

Table 2 shows the order of administration of the tests. Informed consent was obtained before testing began. The total battery required approximately two hours to administer. In addition, the FM subjects completed the subject characteristics questionnaire and were given the DSM-IV checklist questions following the battery, which required an additional 10 minutes.

As can be seen from Table 2, Block Design and the PASAT were administered during the time period between the immediate and delayed recall trials of the CVLT. Neither of these measures involved memory for words, and thus, should not have interfered with performance on the delayed recall trial of this measure. During the CFT delay, the immediate memory reproduction of the CFT, Information, WAIS-RNI Information, Comprehension subtest, BNT, and ACT tests were administered. None of the measures administered following the CFT immediate recall trial involved visuospatial memory, and thus, should not have interfered with the delayed recall trial of the CFT.

Sections 2 and 3 were administered in a counterbalanced order to control for possible effects of pain, fatigue, and malaise on neuropsychological tests given later in the battery. These sections required the same amount of time to administer. In addition, subjects were given a break prior to beginning each new section so that they could rest and/or move around to manage these symptoms.

Table 2

Order of Test Administration

Section 1

Informed Consent
Dolorimeter Testing
Visual Analogue Scales

Section 2

Controlled Oral Word Association (letter "c")
Animal Naming
California Verbal Learning Test
Block Design
PASAT
California Verbal Learning Test – Long Delay

(5 Minute Break)

Section 3

Rey Osterrieth Complex Figure Test (CFT) – Copy and Immediate Recall
Boston Naming Test
Auditory Consonant Trigrams
Information Subtest
WAIS-RNI (Information Subtest)
Comprehension Subtest
CFT – Delayed Recall

(5 Minute Break)

Section 4

Profile of Mood States
SF-36
DSM-IV Checklist (FM Subjects Only)
Subject Characteristics Form (FM Subjects Only)

Hypotheses

Intellectual Functioning in FM

The following hypotheses were proposed for the current study:

1. Based on previous findings of no differences between FM and control groups on tests of intellectual functioning, it was hypothesized that no such differences would occur in the current study.

Effects of FM on Langauge Functioning

2. Based on FM subjects' complaints of difficulties with word-finding, it was hypothesized that the FM group would perform significantly worse on the BNT than controls.
3. It was also hypothesized that, due to word-finding complaints and apparent difficulties with recall, FM subjects would benefit from phonetic cueing on the BNT significantly more often than controls.
4. FM subjects were also hypothesized to perform significantly worse on word list generation tasks (animals and letter 'c') due to the language complaints described above. Although the number of perseverations made on these measures was calculated, it was not expected that the two groups would differ on this score.

Effects of FM on Attentional Functioning

5. On the PASAT, a significant group by trial interaction was hypothesized because it was expected that FM subjects would perform significantly, progressively worse across the four trials of this measure as compared to controls. In other words, the FM group was expected to have greater difficulty than controls as the task became harder. This hypothesis was based on FM subjects' complaints of difficulties with distractibility interfering with memory abilities.
6. Similar performance was expected on the ACT in which a significant group by trial interaction would occur for the same reasons discussed for the PASAT task.

Effects of FM on Memory Functioning

7. On the Information subtest, it was expected that the FM group would perform significantly worse than controls. Although FM subjects have performed normally on verbal subtests of the WAIS-R in previous studies, this particular subtest requires remote recall of information. Thus, this group's complaint of difficulties with recall was expected to affect performance on this measure.

8. It was also hypothesized that FM subjects would benefit from cueing significantly more than controls on the WAIS-RNI, due to proposed difficulties with recall of information.

9. On the ROCF, a group by trial interaction was hypothesized in that the FM group was expected to perform progressively worse than controls across the immediate and delayed trials of this measure. This hypothesis was based on previous findings of difficulties on this measure among FM patients.

10. It was hypothesized that, due to complaints of distractibility interfering with the ability to learn, and difficulty retrieving information, the FM group would perform significantly worse on most of the CVLT variables. Number of items recalled on the learning trials and the long delayed free recall trial were expected to be significantly less for FM versus control subjects. There was no a priori reason to hypothesize that the FM group would use semantic clustering less often than controls, and thus, no difference was necessarily expected between the groups for this score. However, FM subjects were expected to be more susceptible to proactive interference, yielding poorer scores on percent change in performance from Trial 1, List A to List B. Also, FM subjects were expected to perform worse on short delay free recall than controls due to the effects of retroactive interference.

11. Because it was hypothesized that FM subjects may have a retrieval deficit, no differences in recognition abilities between the two groups were proposed.

12. Finally, percentage of intrusions on short delay cued recall was compared between the two groups because previous findings indicated that head injured patients generated significantly more intrusions than controls on this trial. However, there is no a priori reason to expect that this difference will occur between FM and control groups in the current study. Thus, no significant difference was expected between the groups for this score.

Effects of Anxiety on Cognitive Functioning in FM

13. Anxiety, which also can occur in FM, has been found to affect working memory and sustained attention. Thus, it was expected that anxiety in FM would negatively correlate with performance on measures involving memory and attention, such as the PASAT and ACT.

Effects of Depression on Cognitive Functioning in FM

14. Depression was expected to be present in some of the FM subjects. Depression has been found to affect memory and attentional abilities, and thus, it was expected that depressed FM patients would perform significantly worse than nondepressed FM subjects on the memory and attentional measures used in the current study.

Effects of Antidepressant Medication on Cognitive Functioning in FM

15. It was also expected that some of the FM patients would be on antidepressant medication. Because some antidepressants, specifically the more sedating ones, have been found to affect attention, memory, and learning abilities, it was expected that patients on sedating antidepressants would perform significantly worse than controls on the memory and attentional measures.

Effects of FM Symptoms on Cognitive Functioning

16. Pain can affect ability to pay attention, as can fatigue. Thus, these symptoms were expected to negatively correlate with performance on the cognitive measures in the FM group.
17. It was hypothesized that a negative correlation would occur between severity of illness and scores on cognitive measures because subjects with more severe cases of the illness would be expected to have a higher level of pain, fatigue, malaise, and possibly, depression and anxiety.

CHAPTER 3
RESULTS

Demographic and Illness-Related Variables

Examination of information obtained from the subject characteristics form showed that each of the FM subjects met Yunus et al. (1989) criteria for FM in addition to meeting ACR criteria. Yunus et al. (1989) suggested that, for a diagnosis of FM to be made, the patient must have the presence of two or more historical variables, four or more tender points, pain at four or more anatomical sites, and have no underlying condition that could be responsible for the symptoms of FM. The historical variables included having pain at seven or more tender points, general fatigue, poor sleep, anxiety/tension, irritable bowel syndrome, and feeling as if one "hurt all over." Twenty of the 24 FM subjects endorsed all six historical variables, and the remaining four subjects endorsed four historical variables. All subjects met the remaining criteria. Thus, the entire FM sample met Yunus et al. (1989) criteria for FM.

The subject characteristics form also required FM subjects to list any medications taken regularly (Table 3), and specifically inquired as to what, if any, medications had been taken on the day of testing. For pain management, eight subjects were taking nonsteroidal antiinflammatory drugs (NSAIDS), one was on an anticonvulsant (Neurontin), and seven were taking opioids (Ultram or Lortab). For sleep difficulties, six subjects took benzodiazepines and nine were on a low dosage of a sedating antidepressant (specifically, Trazodone, Doxepin, Elavil, or Pamelor). Five subjects took muscle relaxants, 14 were taking a therapeutic dosage of nonsedating antidepressant (specifically, Effexor, Prozac, Zoloft, or Paxil), and 11 were on estrogen replacement therapy. It is not known if nonsedating antidepressants (at therapeutic dosages) had been prescribed for depression, pain, sleep difficulties, or some combination of these symptoms.

Table 3

Medications Used by FM Group

Medication Type	Number of Subjects
NSAID	8
Opioid	7
Anticonvulsant	1
Benzodiazepine	6
Antidepressant (low dose, sedating)	9
Antidepressant (therapeutic dose, nonsedating)	14
Muscle Relaxant	5
Estrogen Replacement Therapy	11

On the day of testing, eight subjects had taken a NSAID and three had taken an opioid for pain, and all 14 subjects who were on a full dosage of an antidepressant had taken this medication. No subject had taken a benzodiazepine, an anticonvulsant, or a muscle relaxant prior to testing.

The subject characteristics form also inquired about the length of time since the FM subject had been diagnosed and how long the subject had been experiencing the symptoms of FM (which designated their illness duration). The average length of time since diagnosis was 3.8 years for this sample, and the average duration of symptoms was 7.6 years. Forty-one percent of FM subjects had a clinical diagnosis of depression according to DSM-IV criteria.

Demographic data for both the FM and control samples are presented in Table 4. The FM group consisted of one African American and 23 Caucasian subjects, ranging in age from 24 to 60 years, with a mean age of 45.1 years. Education levels of patients in this group ranged from

12 to 18 years, with a mean education level of 14.0 years. The healthy control group was made up of one African American and 23 Caucasian subjects, ranging in age from 24 to 59 years, with a mean age of 44.8 years. Education levels ranged from ten to 20 years in this group, with a mean education level of 14.5 years. Two-tailed t-tests revealed no significant differences between the two groups for age, $\underline{t}(46) = .107$, $\underline{p} > .05$, or education level, $\underline{t}(46) = .186$, $\underline{p} > .05$.

Table 4

Descriptive Statistics for Age and Education Variables

Variable	N	FM Group	Control Group	$\underline{t}^a$	$\underline{p}$
Age	24	45.08(9.50)	44.79(9.33)	.107	.915
Education	24	13.96(1.92)	14.50(2.64)	.186	.420

Note. Age and education listed in years (standard deviation in parentheses).
$^a\underline{df} = 46$.

Descriptive statistics for the three illness-related variables are presented in Tables 5, 6, and 7. One-tailed tests were used because, by definition, the control group was expected to be healthy and free of chronic pain, depression, and anxiety, and therefore, was expected to score lower on VAS testing and higher on dolorimeter testing and the SF-36 Health Survey.

Results of t-tests performed on the severity of illness variables are shown in Table 5. Levene's test for equality of variances between groups was performed initially on all analyses to determine if the "equal variances" or "unequal variances" $\underline{t}$ statistic would be used. Means were significantly different for all of the variables at an alpha level of .001, with the exception of the MH scale, which was significant at the .01 alpha level. As expected, the FM group had lower pain tolerance than the control group for both tender points (DOLMEAN) and control points (CONTMEAN). For the FM group, the mean pressure to produce pain at both the tender points and the control points fell below the clinical cut-off of four kg, indicating that the control points for this sample were not diagnostically useful. A paired sample t-test demonstrated that there was

Table 5

Descriptive Statistics for the Severity of Illness Variables

Variable	FM Group	Control Group	t[a]	1-tailed p
		Dolorimeter Testing[b]		
DOLMEAN	2.28(1.15)	5.06(1.20)	-8.20	.000
CONTMEAN	3.08(1.6)	5.99(2.17)	-5.28	.000
		SF-36 Health Survey[c]		
SF6MEAN	33.38(14.94)	85.58(10.88)	-13.84	.000
PF	37.50(22.51)	93.13(7.49)	-11.49	.000
RFPHYS	11.46(19.48)	91.58(17.64)	-14.94	.000
BP	29.25(16.23)	81.67(17.66	-10.71	.000
GH	43.96(18.21)	86.08(13.60)	-9.08	.000
V	26.04(19.94)	70.83(14.19)	-8.97	.000
SF	47.37(21.20)	90.10(17.28)	-7.65	.000
RFEMOT	37.49(38.47)	84.73(25.96)	-4.99	.000
MH	61.33(20.25)	77.00(13.46)	-3.16	.002
		Visual Analogue Scales[d]		
VASMEAN	6.70(2.61)	1.06(1.13)	9.71	.000
VASFAT	6.90(3.01)	1.62(2.42)	6.70	.000
VASPAIN	7.78(2.87)	0.67(0.97)	11.51	.000
VALMAL	5.42(3.51)	0.96(1.40)	5.80	.000

Note. [b] mean pressure in kg (standard deviation in parentheses); DOLMEAN = mean amount of pressure to produce pain across 18 tender points; CONTMEAN = mean amount of pressure to produce pain across four control points; [c] transformed score on scale of 0 to 100 (standard deviation in parentheses); SF6MEAN = mean of six physical functioning scales of the SF-36 (SF-36 four-week score); PF= Physical Functioning scale; RFPHYS = Role- Functioning Physical scale; BP = Body Pain scale; GH = General Health scale; V = Vitality scale; SF = Social Functioning scale; RFEMOT = Role-Functioning Emotional scale; MH = Mental Health scale; [d] score on scale of 0 to 15 cm (standard deviation in parentheses); VASMEAN = mean of three VAS scales (VAS time-of-testing score); VASFAT = VAS fatigue rating; VASPAIN = VAS pain rating; VASMAL = VAS malaise rating.

[a] df = 46.

a statistically significant difference between the tender and control points for the FM group [t (23)= -3.809, p = .001]. However, because there was only a one-kg difference between the tender and control point means, it is not likely that this result is clinically meaningful. Fibromyalgia subjects had a mean number of 15 tender points and 2.75 control points. In the control group, neither the tender points nor the control points tested positively, indicating that this group, as a whole, did not meet clinical criteria for FM.

According to the SF-36 Health Survey, the FM group had experienced significantly poorer health for the four-week period prior to testing (SF6MEAN) than the control group. FM subjects had also experienced significantly more limitations in performing daily physical activities (PF) and problems with work due to physical difficulties (RFPHYS), greater body pain (BP), and less energy (V) than controls. The FM group evaluated their general health as being significantly worse (GH) and reported significantly greater interference with social activities due to physical problems (SF). They also reported significantly more difficulties with work due to emotional problems (RFEMOT) and acknowledged feeling significantly more depressed and anxious than the control group (MH) over the four weeks prior to testing.

Visual inspection of histograms and frequency tables generated separately for the two groups on each of the illness-related variables found that several of them were either skewed or noncontinuous. Therefore, the nonparametric equivalent of the t-test (Mann-Whitney U Test) was performed on these variables, the results of which are presented in Table 6. Mean ranks for the skewed and noncontinuous SF-36 and VAS variables were also significantly different at an alpha level of .001 with nonparametric analysis.

Because the control group had been screened for medical problems, a comparison of the FM group with this sample does not accurately reflect the true difference between the health of patients with FM and the general population. Therefore, one-tailed t-tests were carried out between the FM group and the 45 to 54 year old, female normative group (N=193) in the SF-36 Health Survey manual (Ware, 1993). The results of this analysis are shown in Table 7. A one-tailed t-test was used because it was expected that the general population would be healthier than

Table 6

Descriptive Nonparametric Statistics for Nonnormal and Hetero Severity of Illness Variables

Variable	FM Mean Rank	Control Mean Rank	Mann-Whitney U[a]	1-tailed p
Dolorimeter Testing				
DOLMEAN	12.96	36.04	11.00	.000
CONTMEAN	15.46	33.54	71.00	.000
SF-36 Health Survey				
SF6MEAN	12.63	36.38	3.00	.000
PF	12.58	36.42	2.00	.000
RFPHYS	12.83	36.17	8.00	.000
BP	13.04	35.96	13.00	.000
GH	13.23	35.77	17.50	.000
SF	14.48	34.52	47.50	.000
RFEMOT	16.94	32.06	106.50	.000
Visual Analogue Scales				
VASFAT	34.58	14.42	46.00	.000
VASPAIN	36.35	12.65	3.50	.000
VALMAL	34.10	14.90	57.50	.000
VASMEAN	36.04	12.96	11.00	.000

Note. DOLMEAN = mean amount of pressure in kg to produce pain across 18 tender points; CONTMEAN = mean amount of pressure in kg to produce pain across four control points; SF6MEAN = mean of 6 physical functioning scales of the SF-36 (SF-36 4-week score); PF= Physical Functioning scale; RFPHYS = Role- Physical scale; BP = Body Pain scale; GH = General Health Scale; SF = Social Functioning scale; RFEMOT = Role-Emotional scale; VASFAT = VAS fatigue rating; VASPAIN = VAS pain rating; VASMAL = VAS malaise rating; VASMEAN = mean of 3 VAS scales (VAS time-of-testing score).

[a] n = 48.

the FM group. All of the comparisons were significant at the $p < .0005$ level of significance, indicating that the FM group reported poorer physical and mental health than females of the same age from the general population.

Table 7
Comparison of SF-36 Scores[a] Between the FM Group and the General Population

Variable	FM Group	Normative Group	t^b	1-tailed p
PF	37.50(22.51)	82.86(21.72)	-10.15	$p < .0005$
RFPHYS	11.46(19.48)	79.93(35.38)	-9.29	$p < .0005$
BP	29.25(16.23)	72.14(23.34)	-9.30	$p < .0005$
GH	43.96(18.21)	70.48(20.58)	-6.15	$p < .0005$
V	26.04(19.94)	60.62(21.32)	-7.74	$p < .0005$
SF	47.37(21.20)	82.71(20.84)	-7.98	$p < .0005$
RFEMOT	37.49(38.47)	81.92(33.34)	-6.20	$p < .0005$
MH	61.33(20.25)	74.36(18.08)	-3.45	$p < .0005$

Note. [a] transformed score on scale of 0 to 100 (standard deviation in parentheses); PF= Physical Functioning scale; RFPHYS = Role- Functioning Physical scale; BP = Body Pain scale; GH = General Health scale; V = Vitality scale; SF = Social Functioning scale; RFEMOT = Role-Functioning Emotional scale; MH = Mental Health.
[b] df = 215.

Finally, at the time of testing, the FM group was more significantly ill (VASMEAN) than controls. Specifically, this group was experiencing significantly more pain (VASPAIN), fatigue (VASFAT), and malaise (VASMAL) than the control group (Table 4).

One-tailed t-tests were used to test the difference between the FM and control groups on the Tension-Anxiety and Depression-Dejection scores of the POMS (Table 8). Again, it was expected that, because the control group had been screened for anxiety and depression as a requirement for participation in the study, they would score lower than the FM group on these variables. Means were found to be significantly different at an alpha level of .001 for POMS Tension-Anxiety and at an alpha level of .01 for POMS Depression scale, indicating that the FM subjects were significantly more depressed and anxious than the controls.

Table 8

Descriptive Statistics of the Mood Measure (Profile of Mood States)

Variable	FM Group	Control Group	t^a	1-tailed p
POMSTA	13.33(8.21)	4.04(6.08)	4.45	.000
POMSD	14.50(14.32)	6.46(6.32)	2.52	.009

Note. POMSTA = Tension-Anxiety scale (possible score range of 0-36, standard deviation in parentheses); POMSD = Depression-Dejection scale (possible score range of 0-59, standard deviation in parentheses).
^{a}df =46.

Visual inspection of histograms and frequency charts generated separately for the FM and the control group for these variables demonstrated that both POMSD and POMSTA were severely skewed in the control group. Therefore, the Mann Whitney U Test was used to nonparametrically analyze differences between the groups. Mean ranks are displayed in Table 9. The FM group was again found to be significantly more anxious at the .001 level of significance and more depressed (although at a slightly lower significance level of .05) than the control group.

The mean FM scores on the POMS were also compared to norms collected from 1005 female medical outpatients made up of adults diagnosed with chronic fatigue syndrome, severe recurrent sinus headaches, and various other unspecified medical conditions (McNair et al., 1992). The age range of the normative sample was not specified. A two-tailed t-test was used because it was not possible to determine a priori if the FM group would score higher or lower than the medical normative group. The FM group was significantly more depressed (POMSD) and anxious (POMSTA) than this normative group at the $p < .02$ significance level (Table 10).

Table 9

Nonparametric Descriptive Statistics of Mood Measure (Profile of Mood States)

Variable	FM Group	Control Group	Mann-Whitney U[a]	1-tailed p
POMSTA	33.21	15.79	79.00	.000
POMSD	29.08	19.92	178.00	.012

Note. POMSTA = Tension-Anxiety scale (possible range of scores is 0-36, standard deviation in parentheses); POMSD = Depression-Dejection scale (possible range of scores is 0-59, standard deviation in parentheses).

[a] $n = 48$.

Table 10

FM Group POMS Scores Compared to Norms from a Medical Population

Variable	FM Group	Normative Group	t[a]	2-tailed p
POMSTA	13.33(8.21)	8.82(8.48)	2.56	$p < .02$
POMSD	14.50(14.32)	8.10(12.88)	2.40	$p < .02$

Note. POMSTA = Tension-Anxiety scale (possible range of scores is 0-36, standard deviation in parentheses); POMSD = Depression-Dejection scale (possible range of scores is 0-59, standard deviation in parentheses).

[a] df=1027.

Results from previous studies have been inconsistent regarding whether or not significant differences occurred between FM subjects and controls in levels of anxiety and depression. Some authors have proposed that differences were found only when more severely ill FM subjects were used. To examine whether or not a significant relationship existed between severity of illness and measures of anxiety and depression in the FM group in the current study, Spearman Rank correlations were conducted between the FM group's mean severity of illness score (using the mean of the six SF-36 physical scales) and the POMS-Depression and POMS-Anxiety scores. Neither of these correlations were significant at an alpha level of .05.

It was of interest to determine if patients recruited from Shands Hospital (Rheumatology Clinic) were more severely ill, depressed, or anxious than patients who had been recruited from the community. Therefore, two-tailed t-tests were performed comparing the two groups on the length of symptoms (LENGTHSX), overall severity of illness (SF6MEAN) and level of pain (BP) over the last four weeks, level of pain at the time of testing (VASPAIN), and the mood measures (RFEMOT, MH, POMTA, POMSD).

Results from this analysis (Table 11) demonstrated that the rheumatology subjects had not been ill for a significantly different period of time than the community subjects [$t(22) = -1.17$, $p > .05$], but they had experienced significantly poorer health for the four weeks prior to testing [$t(22) = -2.43$, $p < .05$], and had experienced significantly more body pain during this time [$t(22) = -2.26$, $p < .05$]. They were not experiencing significantly more pain at the time of testing [$t\ (22) = .697$, $p > .05$].

In terms of emotional functioning, on the SF-36, the rheumatology FM subjects reported significantly more problems with work or other daily activities as a result of emotional problems [$t(22) = -3.23$, $p < .05$] but did not indicate that they felt nervous or depressed more often than the community subjects [$t(22) = -1.23$, $p > .05$]. On the POMS, similar results were found in that the rheumatology group was no more depressed [$t(22) = 1.18$, $p > .05$] or anxious [$t = 1.28$, $p > .05$] than the community group.

Visual inspection of histograms generated separately for the rheumatology and community groups indicated that all of the above variables except for VASPAIN were nonnormal. Because of this, Mann-Whitney U tests were used to again compare the groups on these variables. Nonparametric results did not differ from the parametric findings described above.

Table 11

Comparison of Severity of Illness and Mood Disturbance between FM Patients Recruited from the Shands Hospital Rheumatology Clinic[a] Versus the Community[b]

Variable	Rheumatology	Community	t[c]	2-tailed p
LENGTHSX	5.65(3.20)	10.37(6.65)	-1.17	.115
SF6MEAN	29.01(15.09)	43.87(8.17)	-2.43	.024
BP	24.82(15.13)	40.00(14.47)	-2.26	.034
VASPAIN	8.01(3.08)	7.20(2.36)	.697	.497
RFEMOT	23.52(30.65)	71.41(35.65)	-3.23	.003
MH	58.12(21.59)	69.14(15.09)	-1.23	.233
POMSTA	14.59(8.70)	10.29(6.42)	1.18	.252
POMSD	16.24(16.40)	10.29(6.29)	1.28	.213

Note. LENGTHSX = number of years subject had experienced symptoms of FM; SF6MEAN = mean of 6 physical functioning scales of the SF-36 (SF-36 four-week score); BP = Body Pain scale; VASPAIN = level of pain at time of testing; RFEMOT = Role-Functioning Emotional scale; MH = Mental Health Scale; POMSTA = Tension-Anxiety scale of the POMS; POMSD = Depression-Dejection scale of the POMS.
[a]n = 17. [b]n = 7.
[c]df = 22.

Neuropsychological Variables

All neuropsychological variables were examined for departure from normality by visually examining histograms generated separately for the two groups and by performing Shapiro-Wilks testing on residuals derived from a one-way ANOVA of each measure, with group considered as a between-subjects factor. Levene's test of equality of error variances was used to determine if the variance between the FM and control groups was significantly different for any variable. Variables that did not appear normally distributed or that exhibited heteroscedasticity (nonhomogenous variance) were then transformed using the arcsine-square root transformation. However, this successfully normalized only one of the variables, as determined from re-examination with the Shapiro-Wilks test. Further evaluation using the log-transformation, when possible, normalized only one additional variable. Thus, variables that did not become normally distributed and homoscedastic with transformation were analyzed using nonparametric statistics, and the remaining variables were analyzed parametrically. All analyses and tests for normality and homoscedasticity were performed using SPSS Graduate Pack 8.0 for Windows.

One-tailed tests were used on comparisons of variables when the FM group was expected to perform worse than the controls. When expectations were less clear, two-tailed tests were performed.

Analyses of Intellectual Screening Variables

Hypothesis 1

To test the hypothesis that there would be no significant differences in intellectual functioning between the FM and control groups, two-tailed t-tests were performed on the Block Design and the Comprehension subtests of the WAIS-R. Both of these variables appeared normally distributed and homoscedastic, and thus, parametric statistics were used. As shown in Table 12, there was no significant difference between the groups on either of the subtests. Thus, there was no evidence to suggest that the two groups were significantly different in level of intellectual functioning. Visual inspection of Block Design and Comprehension mean scores indicated that both the FM and the control group scored in the normal range for these subtests (Wechsler, 1981).

Analyses of Language Variables

Because several comparisons were made during analysis of the language variables, it was necessary to control the Type I error rate. A Bonferroni adjustment (Lehman, 1995) was done in

Table 12

Descriptive Statistics for the Intellectual Screening Variables

Variable	FM Group	Control Group	t^a	2-tailed p
BDAGE	10.4(3.1)	11.8(3.1)	-1.57	.124
COMPAGE	9.6(3.4)	10.6(2.4)	-1.19	.238

Note. BDAGE = age-corrected Block Design subtest scaled score (standard deviation in parentheses); COMPAGE = age-corrected Comprehension subtest scaled score (standard deviation in parentheses).
[a]df = 46.

which the .05 alpha level was divided by the number of language analyses conducted. Thus, an alpha level of .007 was used to control for Type I errors among the seven language analyses. FM and control group means and standard deviations for the language variables are displayed in Table 13. Due to nonnormality and heteroscedasticity, all of these variables, with the exception of Animals and Letter C, were examined using nonparametric statistics. Animals was successfully transformed using the log transformation, and Letter C did not need to be transformed. Thus, the transformed ANIMALS and LETTER C variables were analyzed parametrically.

Hypothesis 2

To test the hypothesis that FM subjects would be impaired on the BNT as compared to controls, a one-tailed Mann Whitney U test was used. A one-tailed test was used because it was expected that FM subjects would perform worse than controls based on FM subjects' complaints of word finding difficulty. Results of the nonparametric language analyses are listed in Table 14.

Table 13

Descriptive Statistics for the Language Variables

Variable	FM Mean*	Control Mean*
BNT	55.3(3.0)	55.1(4.0)
PHONCUE	4.8(3.0)	4.9(3.9)
BNTPROP	.60(.27)	.73(.33)
LETTER C	12.8(3.8)	14.0(5.4)
LET C PERSEV	.17(.48)	.38(.71)
ANIMALS	16.8(4.6)	20.5(5.9)
ANIMALS PERSEV	.17(.48)	.38(.58)

Note. *standard deviation in parentheses; BNT = number correct on the Boston Naming Test; PHONCUE = number of times subject required cueing on the BNT; BNTPROP = proportion of times subject benefited from cueing on the BNT; LETTER C = number of words beginning with the letter 'c' generated; LET C PERSEV = number of perseverations on LETTER C; ANIMALS = number of animals generated; ANIMALS PERSEV = number of perseverations on ANIMALS.

Table 14

Nonparametric Analyses of the Language Variables

Variable	FM Mean Rank	Control Mean Rank	Mann Whitney U^a	1-Tailed p	2-Tailed p
BNT	24.02	24.98	276.5	.406	---
PHONCUE	25.00	24.00	276.0	.803	---
BNTPROP	21.33	27.67	212.0	.108	---
ANIMALS PERS	22.10	26.90	230.5	---	.105
LET 'C' PERSEV	22.94	26.06	250.5	---	.255

Note. BNT = Boston Naming Test; PHONCUE = number of times subject required cueing on the BNT; BNTPROP = proportion of times subject benefited from cueing on the BNT; ANIMALS PERS = number of perseverations on Animals; LET C PERSEV = number of perseverations on Letter C.

[a] $n = 48$.

As shown, mean ranks for the BNT were not significantly different between the two groups. Thus, the hypothesis that FM subjects would display naming difficulties was not confirmed. Visual inspection of mean scores indicated that neither the FM nor the control group scored in the impaired range on this measure according to age-appropriate norms published in Goodglass and Kaplan (1983).

Hypothesis 3

It was hypothesized that, due to FM subjects' complaints of difficulties with recall, this group would exhibit a retrieval deficit, and thus, would benefit from phonemic cueing more often than controls on the BNT. To compute the proportion of times a subject benefited from cueing (BNTPROP), the number of items correct following cueing was divided by the number of times the subject needed cueing (PHONCUE). However, prior to determining whether or not the groups differed on the proportion of times they benefited from cueing, it was necessary to determine whether or not the groups were significantly different with respect to the number of opportunities they had to benefit from cueing. To do this, a one-tailed Mann Whitney U test was used to compare the mean number of cues (PHONCUE) that each group required. The results of this analysis demonstrated that the mean ranks were not significantly different for this variable (Table 14). Thus, the proportion correct following cueing could now be compared without having to adjust first for differences between the groups in number of opportunities they had for cueing. Subsequently, the group mean ranks for the proportion of times the two groups benefited from cueing were not found to be significantly different (BNTPROP; Table 14). Thus, FM and control subjects did not benefit differentially from phonemic cueing on the BNT, and Hypothesis 3 was not confirmed.

Hypothesis 4

To test the hypothesis that FM subjects would perform significantly worse than controls on tests of word list generation, one-tailed tests were used. A t-test comparing FM and control subjects on the transformed ANIMALS variable was significant at an alpha level of .05 (Table 15). However, after making the Bonferroni adjustment, this difference became nonsignificant, and thus, this hypothesis was not confirmed. The control group mean and the FM group mean for this task fell within one standard deviation of the normative mean according to age-and education-matched norms (Tombaugh, Kozac, & Rees, as cited in Spreen & Strauss, 1998). Also, the FM group mean fell within one standard deviation of the mean of the control group used in the present study. Thus, neither the FM nor the control group appeared to perform in the clinically impaired range on this measure.

Table 15

Parametric Analyses of Language Variables

Variable	t^a	1-tailed p
ANIMALS	-2.39	.010
LETTER C	-.871	.194

Note. ANIMALS = number of animals generated; LETTER C = number of words beginning with the letter ‘c’ generated.
[a]df =46.

To investigate differences in the number of perseverations on the animal naming task (ANIMALS PERS; Table 14), a two-tailed Mann Whitney U test was used because there was no a priori reason to suggest that FM subjects would make more perseverative errors than controls. Mean ranks were not found to be significantly different for the two groups, and thus, there was no evidence to suggest that FM subjects exhibited greater perseverations on this task.

To evaluate performance on Letter C, a one-tailed t-test was performed. As shown in Table 15, the mean scores for the FM and control groups were not significantly different, and thus, Hypothesis 4 was not confirmed. The FM group scored less that one standard deviation below the control group, suggesting that FM subjects were not clinically impaired on this measure.

Mean ranks were not significantly different for the number of perseverations made on this task (LET C PERSEV; Table 14), indicating there is no evidence to suggest that FM and control subjects generated a significantly different number of perseverations on this task.

Analyses of Attentional Measures

To analyze performance on the attentional measures (the PASAT and the ACT), repeated measures ANOVAs (RMAs) were conducted in which group was considered as a between-subjects factor, and trial was considered as a within-subjects factor. Descriptive statistics for these variables are shown in Table 16. Because scores for both of these tests were slightly skewed, RMAs were conducted using both the untransformed responses and the arcsine-square root transformed responses. Because results from the analyses of the transformed and the untransformed response variables led to the same conclusions, only the untransformed results will be reported below.

To determine if the univariate or multivariate form of RMA should be performed, individual PASAT and ACT profiles were examined graphically to assess the degree of parallelism among the individual profiles within each group. Also, univariate RMAs were conducted on both the PASAT and the ACT so that the validity of using this approach could be evaluated. Validity was evaluated by examining (1) the pairwise correlations among the trials, (2) the results of the sphericity test, and (3) the Greenhouse-Geisser and Huynh-Feldt Epsilon-adjusment factors for the F-test degrees of freedom. When these methods proved univariate analysis to be inappropriate, the multivariate form of RMA was performed. Following analysis

Table 16

Descriptive Statistics for the Attentional Measures

Variable	FM Mean*	Control Mean*
PASAT Trial 1	82.5(16.3)	83.6(14.4)
PASAT Trial 2	67.8(15.5)	73.4(18.2)
PASAT Trial 3	59.9(18.4)	66.4(17.2)
PASAT Trial 4	48.3(15.6)	57.3(18.4)
ACT 3" Delay	74.2(12.2)	82.8(10.9)
ACT 9" Delay	60.2(20.3)	71.2(18.5)
ACT 18" Delay	56.1(20.7)	61.3(20.3)

Note. *mean listed as the percent correct; standard deviation in parentheses; PASAT = Paced Auditory Serial Addition Test; ACT = Auditory Consonant Trigrams.

with RMA, a linear polynomial contrast was performed on both the PASAT and the ACT to determine if any trend occurred across the trial mean response profiles of the groups.

Hypothesis 5

RMA was hypothesized to demonstrate that, on the PASAT, the FM group's mean score of the four trials would be significantly lower than that of the control's, yielding a significant group main effect. In addition, a significant trial main effect was expected in that the groups were hypothesized to perform significantly differently on the four trials. Finally, the pattern of performance over the four trials was expected to be different for the two groups (causing a significant group by trial interaction).

Linear polynomial contrast was hypothesized to show that the groups would perform progressively worse over the four trials (trial effect). Also, it would demonstrate that the proposed decline in performance would be significantly greater for the FM subjects as compared to controls (a group by trial trend interaction).

Visual inspection of the individual profiles for the FM and control groups on the PASAT suggested that the profiles were somewhat parallel. However, the test for sphericity was significant at an alpha level of .05, indicating that the pairwise correlations among the trials differed significantly. Thus, univariate analysis of this variable was not appropriate, and the multivariate form of the RMA was subsequently conducted.

Mean response profiles for the FM and control groups are shown in Figure 1a. No significant trial by group interaction was found following multivariate analysis [$\underline{F}(3,44) = .905$, $\underline{p} = .45$]. Trial mean response profiles compared between groups via linear polynomial contrasts also did not differ significantly ($\underline{p} = .108$). A significant trial main effect was found [$\underline{F}(3,44) = 54.98$, $\underline{p} = .0001$], as well as a significant decreasing trend across the four trial mean response profiles by linear polynomial contrast ($\underline{p} = .0001$), with both groups showing a decline in percent correct across trials. However, there was no significant group effect [$\underline{F}(1,46) = 1.69$, $\underline{p} = .20$]. Thus, FM and control subjects did not differ in the mean percent correct on the PASAT, nor did the pattern of performance across the four trials differ significantly between the groups. Therefore, Hypothesis 5 was not confirmed.

Visual inspection of mean FM and control scores as compared to normative data for the PASAT provided by Stuss, Stethem, and Pelchat (1988) indicated that all scores fell within one standard deviation of mean norms. Also, FM subjects' mean scores fell within one standard deviation of the control group means. Thus, it does not appear the either the FM or the control group performed in the clinically impaired range on this measure.

Hypothesis 6

On the ACT, the same pattern of performance was hypothesized to occur as was hypothesized for the PASAT. Visual inspection of the individual ACT profiles for the FM and control groups suggested that the profiles were parallel. Univariate analysis of this measure proved to be valid in that the test for sphericity was not significant at the .05 alpha level, the

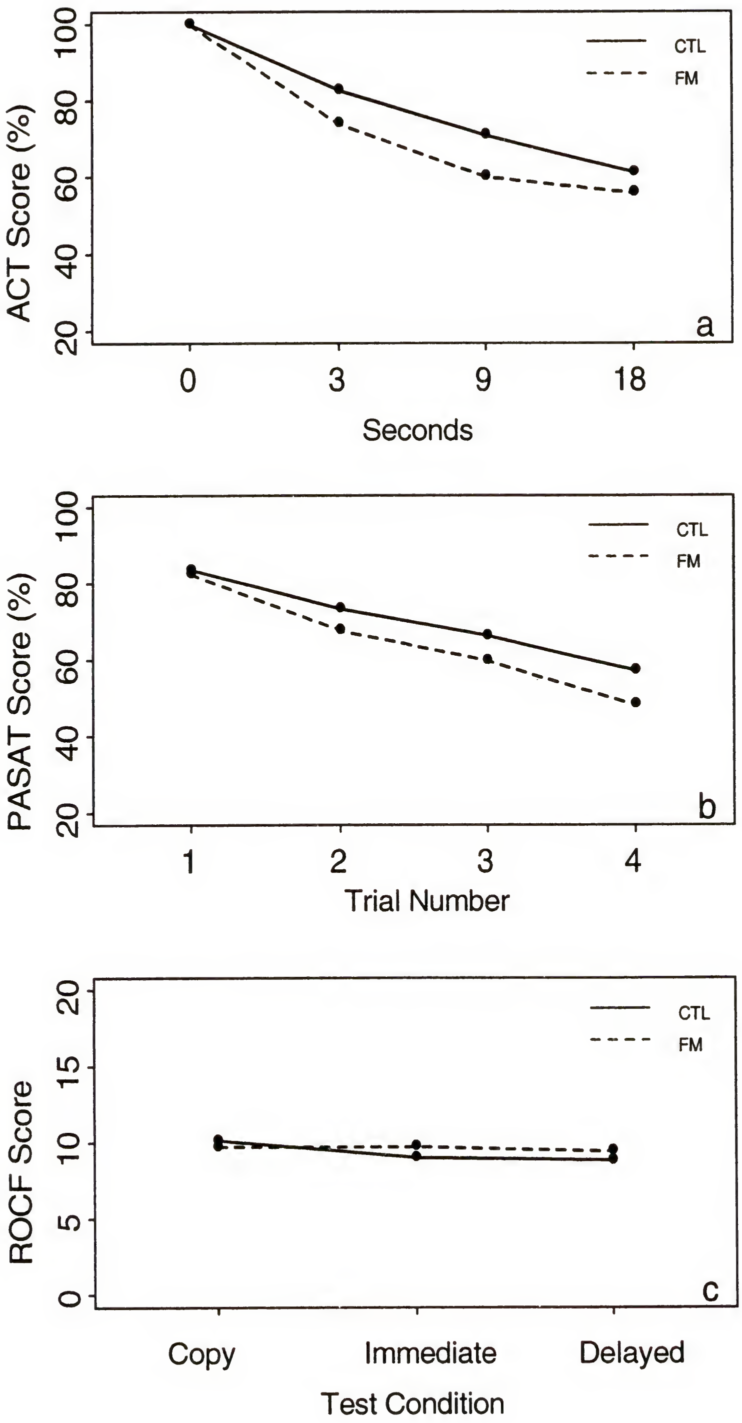

Figure 1. Mean Response Profiles for the FM and Control Groups on the a: Auditory Consonant Trigrams (ACT), b: Paced Auditory Serial Addition Task (PASAT), and c: Rey Osterrieth Complex Figure (ROCF).

pairwise correlations were similar among the three trials, and the Greenhouse-Geisser and Huynh-Feldt Epsilon adjusted p values were similar to unadjusted p values. Thus, it appeared that the assumptions of the univariate form of the RMA were met.

Mean response profiles for the FM and control groups are shown in Figure 1b. The univariate RMA failed to demonstrate a significant trial by group interaction [$F(2,92) = .57$, $p = .567$], and trial mean response profiles compared between groups via linear polynomial contrast did not differ significantly ($p = .55$). A significant trial effect was found [$F(2,92) = 27.47$, $p = .0001$], as well as a significant decreasing trend in the percent correct across trials for both groups ($p = .0001$). Also, a significant group main effect was found [$F(1,46) = 4.25$, $p = .045$]. Thus, the hypotheses that the groups would perform significantly different on, and progressively worse across, the three trials of the ACT (a trial main effect), and that the FM group would perform significantly worse than controls on the three trials of this measure (a group main effect), were confirmed. However, the hypothesis that the decline in performance across the trials would be significantly different for the FM group as compared to controls was not confirmed.

Visual inspection of mean FM and control scores for the ACT for the three trials indicated that both groups scored within one standard deviation of age-appropriate norms provided by Stuss et al (1988), with the exception of the ACT 9” Delay. On this trial, the FM subjects scored 1.2 standard deviations below the normative mean. FM scores for the three trials fell within one standard deviation of that of normal controls’ used in the present study.

Analysis of Memory Measures

Hypothesis 7

Descriptive statistics for the memory measures are shown in Table 17. It was hypothesized that FM subjects would perform significantly worse on the Information subtest of the WAIS-R due to this group’s proposed difficulties with retrieval of information. Comparison of the Information subtest of the WAIS-R using a one-tailed t-test was possible because this variable was both normally distributed and heteroscedastic. Results of this analysis are shown in

Table 17

Descriptive Statistics for the Memory Measures

Variable	FM Mean*	Control Mean*
ROCFCOPY	9.7(2.1)	10.2(1.5)
ROCFIMMED	9.8(2.9)	9.0(3.0)
ROCFDELAY	9.5(3.0)	8.9(3.4)
INFORMATION	10.3(2.0)	10.7(2.7)
NUMBWRONG	9.5(3.5)	8.7(4.6)
WAIS-RNI	.46(.21)	.46(.20)
CVLT1	7.6(1.8)	8.3(1.9)
CVLT 1-5	55.7(10.7)	56.2(10.5)
SEMANTIC CLUSTER	2.3(1.0)	2.3(.90)
PERCHANGE A to B	-3.9(26.8)	-14.9(23.8)
PRSDFR	79.4(19.2)	85.0(13.1)
PRSDCR	93.3(14.1)	95.5(8.1)
PRLDFR	87.1(18.4)	85.3(13.6)
PRLDCR	92.7(14.7)	94.4(12.2)
PISDCR	3.8(8.5)	2.4(5.5)
DISCRIMIN	94.3(5.5)	96.5(4.3)

Note. *standard deviation in parentheses; ROCF = Rey Osterrieth Complex Figure; INFORMATION = age-corrected scaled score for the Information Subtest of the WAIS-R; NUMBWRONG = number wrong on WAIS-R Information subtest, and thus, the number of opportunities for cueing on the WAIS-RNI Information subtest; WAIS-RNI = proportion of times benefited from cueing on the Information subtest of the WAIS-R as a Neuropsychological Instrument; CVLT1 = total number correct for the first trial of the California Verbal Learning Test; CVLT1-5 = total number correct for the five learning trials of the CVLT; SEMANTIC CLUSTER = ratio of the observed over the expected number of times semantic clustering was used during the learning trials; PERCHANGE A to B = percent of items recalled on List B as compared to Trial 1, List A; PRSDFR = percent of originally learned items recalled on short delay free recall trial; PRSDCR = percent of originally learned items recalled on short delay cued recall trial; PRLDFR = percent of originally learned items recalled on long delay free trial; PRLDCR = percent of originally learned items recalled on long delay cued recall trial; PISDCR = percent intrusions on short delay cued recall; DISCRIM = discriminability index for recognition trial.

Table 18. The two groups did not significantly differ on this subtest, and thus, this hypothesis was not confirmed. Both groups scored in the normal range for this test according to WAIS-R normative data.

Table 18

Comparison of Memory Measures Analyzed Parametrically

Variable	t[a]	1-tailed p	2-tailed p
INFORMATION	-.605	.274	---
NUMBWRONG	.708	.241	---
WAIS-RNI	-.055	.478	---
CVLT1	-1.424	.081	---
CVLT 1-5	.126	.448	---
SEMANTIC CLUSTER	.024	---	.988
PERCHANGE A to B	1.501	.070	---

Note. INFORMATION = age-correct scaled score for the Information Subtest of the WAIS-R; NUMBWRONG = number wrong on WAIS-R Information subtest, and thus, the number of opportunities for cueing on the WAIS-RNI Information subtest; WAIS-RNI = proportion of times benefited from cueing on the Information subtest of the WAIS-R as a Neuropsychological Instrument; CVLT1 = total number correct for the first trial of the California Verbal Learning Test; CVLT1-5 = total number correct for the five learning trials of the CVLT; SEMANTIC CLUSTER = ratio of the observed over the expected number of times semantic clustering was used during the learning trials; PERCHANGE A to B = percent of items recalled on trial B as compared to Trial A.

[a] df = 46.

Hypothesis 8

It was also hypothesized that the proportion of times subjects benefited from cueing on WAIS-RNI Information subtest would be significantly higher in the FM group than the control group. This test provided multiple choice responses for items missed on the Information subtest, and thus, provided an opportunity to benefit from cueing. The number of items missed on the Information subtest (NUMBWRONG) was first calculated. This number was then divided into the total number correct on the WAIS-RNI Information subtest, yielding the proportion of times a group benefited from cueing (WAIS-RNI). However, prior to calculating this proportion, it was necessary to determine if the groups had gotten a significantly different number of items wrong on the Information subtest (NUMBWRONG). In other words, had they had a significantly different number of opportunities to benefit from cueing. The mean number of items missed on the WAIS-R Information subtest did not differ significantly between the two groups in a one-tailed t-test (NUMBWRONG; Table 18). A one-tailed t-test then found no significant difference between the groups for the mean proportion of times each benefited from cueing (WAIS-RNI; Table 18). Both of these variables met assumptions for the t-test, and were thus analyzed parametrically. Thus, hypothesis 8 was not confirmed.

Hypothesis 9

To evaluate performance on the ROCF, a RMA was conducted in which group was considered as a between-subjects factor, and trial was considered as a within-subjects factor. Because scores for this measure were slightly skewed, the RMA was conducted using both untransformed scores and the arcsine-square root transformed scores. However, because both analyses led to the same conclusions, only the untransformed results will be reported below. The appropriateness of using the univariate versus the multivariate form of the RMA was explored as described earlier. The multivariate form of the RMA was conducted because univariate analysis found that the test for sphericity was significant at an alpha level of .05, indicating that the pairwise correlations among the three trials differed significantly. Following analysis with RMA, a linear polynomial contrast was performed to determine if any trend occurred across the trial mean response profiles of each group.

On the ROCF, a significant group main effect was expected in which the scaled scores on the three trials would be significantly worse in FM subjects as compared to controls. Also, within each group, subjects were hypothesized to perform significantly differently on the three trials (yielding a significant trial main effect), as well as perform progressively worse across the three trials (according to analysis by linear polynomial contrast). Finally, the pattern of performance across the three trials was expected to be significantly different between the groups (causing a significant group by trial interaction), and the proposed decline in the FM group was expected to be significantly greater than for the controls (according to analysis by linear polynomial contrast).

No significant trial by group interaction was found on the ROCF [$F(2,45) = .986$, $p = .381$], and trial mean response profiles compared between groups via linear polynomial contrast also did not differ significantly ($p = .28$; see Figure 1c). Thus, the pattern of performance across trials did not differ significantly between the groups. Also, no significant trial effect was found [$F(2,45) = 1.39$, $p = .260$], as well as no significant decreasing trend in the trial mean response profiles of the groups ($p = .12$). No significant group main effect was found, either [$F(1,46) = .19$, $p = .67$]. Thus, Hypothesis 9 was not confirmed.

Hypothesis 10

It was hypothesized that due to complaints of difficulties with recall and distractibility interfering with the ability to learn, the FM group would perform significantly worse on all of the CVLT variables, with the exception of semantic clustering, percent intrusions made, and ability to discriminate List A from non-List A items (during recognition testing). On these three variables, there were no a priori expectations concerning differences between the groups. One-tailed tests were done on all CVLT variables except for these three, on which two-tailed tests were performed. The CVLT1-5 variable was successfully transformed using the arcsine-square root transformation, and thus, transformed scores were entered into the analysis. However, for descriptive purposes, the means for the untransformed FM and control scores were presented in Table 17. Nonnormal and nonhomogenous variables were analyzed using the Mann Whitney U test.

Results of these analyses are shown in Tables 18 and 19. FM and control subjects did not differ significantly on the number of items recalled on the first trial of the CVLT (CVLT1; Table 18), nor did they differ significantly on the total number of items learned across the first five trials of this measure (CVLT1-5; Table 18). There was no evidence to suggest that FM subjects and controls differed significantly in amount of semantic clustering used (SEMANTIC CLUSTER; Table 18). FM subjects lost no more information due to proactive interference when comparing List A, Trial 1 performance to List B performance (PERCHANGE A to B; Table 18). The groups also did not significantly differ on the percent of items recalled at short delay free recall (PRSDFR; Table 19), short delay cued recall (PRSDCR; Table 19), long delay free recall (PRLDFR; Table 19), or long delay cued recall (PRLDCR; Table 19). Thus, Hypotheses 10 was not confirmed.

Table 19
Comparison of Memory Measures Analyzed Nonparametrically

Variable	FM Group*	Control Group*	Mann Whitney U^a	1-tailed p	2-tailed p
PRSDFR	23.17	25.83	256.0	.254	---
PRSDCR	23.00	26.00	252.0	.225	---
PRLDFR	25.33	23.67	268.0	.339	---
PRLDCR	22.83	26.17	248.0	.200	---
PISDCR	25.81	23.19	256.5	---	.407
DISCRIM	21.19	27.81	208.5	---	.094

Note. *mean rank; PRSDFR = percent of originally learned items recalled on short delay free recall trial; PRSDCR = percent of originally learned items recalled on short delay cued recall trial; PRLDFR = percent of originally learned items recalled on long delay free trial; PRLDCR = percent of originally learned items recalled on long delay cued recall trial; PISDCR = percent intrusions on short delay cued recall; DISCRIM = discriminability index for recognition trial.
^{a}n = 48.

Hypothesis 11

Because FM subjects were proposed to have recall rather than recognition memory difficulties, no significant difference between the groups was expected for performance on the recognition trial. The variable used to test for possible differences on the recognition trial was the discriminability index, which indicates the subject's ability to discriminate between List A items and non-List A items. As hypothesized, no evidence to suggest a significant difference in performance on the recognition trial was found according to analysis with the Mann Whitney U test (DISCRIM; Table 19).

Hypothesis 12

FM and control groups were not expected to be significantly different in percent of intrusions produced during short delay recall. As hypothesized, no evidence to suggest that FM subjects produced more intrusions during short delay cued recall than controls was found according to analysis with Mann Whitney U testing (PISDCR; Table 19).

Effects of Anxiety, Depression, and Medication on Cognitive Functioning in FM

Hypothesis 13

It was hypothesized that anxiety in FM would adversely affect performance on the cognitive memory measures. To examine the relationship between anxiety and cognitive performance in the FM group, one-tailed Pearson correlations (for normally distributed and homoscedastic dependent variables) and one-tailed Spearman Rank correlations (for nonnormally distributed or heteroscedastic dependent variables) were carried out between the scores on the POMS Tension and Anxiety scale and scores on all of the cognitive variables. To control for possible Type I errors, an alpha level of .01 was employed. No significant correlations were found among any of these variables. Pearson correlation and Spearman Rank correlation coefficients and ranged from -.037 to -.223, with significance levels ranging from .432 to .148. Thus, there was no evidence to suggest that anxiety in the FM group affected cognitive functioning, and Hypothesis 13 was not confirmed.

Hypothesis 14

Based on results of earlier studies, it was hypothesized that depressed FM patients would perform significantly worse than nondepressed FM subjects and controls on the memory and attentional measures used in the study. To test this hypothesis, the FM group was divided into a depressed group and a nondepressed group based on whether or not the subjects met DSM-IV criteria for major depression. A one-way ANOVA was then carried out comparing cognitive performance among three groups: FM depressed (FMD), FM nondepressed (FMND), and control subjects. The Kruskal-Wallace test was conducted on nonnormal or heteroscedastic variables. Variables from each cognitive domain [language (BNT, LETTER C, and ANIMALS), attention

(PASATMN4 and ACTMN3), and memory (ROCFDELAY and PRLDFR)] that were thought to best represent the proposed deficits in FM were chosen. Analyses were carried out using the log-transformed ANIMALS scores, but the nontransformed means were listed in Table 20 for descriptive purposes. Results of these analyses are shown in Tables 20 and 21.

Using an alpha level of .05, a one-way ANOVA demonstrated a significant difference among the three groups (Table 20) on ANIMALS [F(2) = 4.10, p = .023] and ACTMN3 [F(2) = 3.62, p = .035]. Pairwise comparisons using the Bonferroni correction demonstrated that the FMD subjects performed significantly worse than controls on ANIMALS, and the FMND subjects performed significantly worse than controls on ACTMN3. No significant differences were found among the three groups for LETTER C, PASATMN4 or ROCFDELAY (Table 20). Also, no significant difference was found among the three groups using the Kruskal-Wallis test for the BNT or PRLDFR (Table 21). Thus, Hypothesis 13, stating that depressed FM subjects would perform significantly worse than nondepressed FM patients, was not confirmed. However, depressed FM subjects performed worse than controls on one of the language measures.

Table 20

Parametric Comparison of FMD, FMND, and Control Groups on Cognitive Variables

Variable	FMD[a]	FMND[b]	Control[c]	F[d]	p	Bonferroni
ANIMALS	14.4(1.7)	17.8(5.1)	20.5(5.9)	4.10	.023	FMD<Control*
LETTER C	11.9(3.3)	13.2(3.9)	14.0(5.4)	.591	.558	---
PASATMN4	59.7(11.7)	66.7(15.7)	70.2(14.7)	1.41	.254	---
ACTMN3	70.8(5.1)	60.5(3.3)	71.8(2.8)	3.62	.035	FMND<Control**
ROCFDELAY	9.9(2.4)	9.3(3.2)	8.9(3.4)	.27	.763	---

Note. Scores for each group listed as means; standard deviations in parentheses; FMD = depressed FM subjects; FMND = nondepressed FM subjects; ANIMALS = number of animals generated; LETTER C = number of words beginning with the letter 'c' generated; PASATMN4 = mean of the four trial scores of the PASAT; ACTMN3 = mean of the three trial scores of the ACT; ROCFDELAY = delay trial score of the ROCF.
[a]n = 7. [b]n = 17. [c]n = 24.
[d]df = 2.
*p = .025. **p = .037.

Table 21

Nonparametric Comparison of FMD, FMND, and Control Groups on Cognitive Variables

Variable	FMD[a] Mean (S.D.)	FMD Mean Rank	FMND[b] Mean (S.D.)	FMND Mean Rank	Control[c] Mean (S.D.)	Control Mean Rank	CHISQ[d]	p
BNT	54.1(3.1)	17.7	55.7(3.3)	26.6	55.1(4.0)	25.0	2.10	.350
PRLDFR	95.9(18.1)	31.7	83.5(17.7)	22.7	85.3(13.6)	23.7	2.26	.323

Note. S.D.= standard deviation; FMD = depressed FM subjects; FMND = nondepressed FM subjects; BNT = Boston Naming Test; PRLDFR = percent recall for the long delay free recall trial of the CVLT.

[a]n = 7. [b]n = 17. [c]n = 24.

[d]df = 2.

FMD subjects performed one standard deviation below the control group mean on ANIMALS. However, their mean score fell 1.5 standard deviations below the age-appropriate normative mean, suggesting mild clinical impairment (Tombaugh et al., as cited in Spreen and Strauss, 1998). However, on the ACTMN3, FMND subjects scored four standard deviations below the control group mean, suggesting clinically significant differences between the control and nondepressed FM subjects on this measure. There are no published norms with which to compare the FM group on the average of the three ACT trials.

To further test the hypothesis that depression would negatively affect performance on the cognitive measures among FM subjects, one-tailed Pearson correlations (for normally distributed and homoscedastic variables) and Spearman Rank correlations (for nonnormally distributed or heteroscedastic variables) were carried out between POMS Depression scale scores and scores from all of the cognitive measures. An alpha level of .01 was used to control for possible Type I errors. No significant correlations were found in the FM group between scores on the POMS Depression scale and the cognitive variables. For the POMS Depression scale, Pearson and Spearman Rank correlation coefficients ranged from .000 to -.436, with significance levels ranging from .500 to .017. Thus, these analyses demonstrated no evidence that depression in the FM group was related to cognitive functioning.

In addition to examining the effects of depression on cognition in the FM group, it also became important to examine any possible effects of depression on cognition in the control group because one control subject scored greater than three standard deviations above the control mean on the Depression scale of the POMS. This occurred despite having screened the controls for depression using DSM-IV criteria. Thus, all of the pairwise comparisons completed in the current study were repeated without this subject. Because results did not differ between analyses that included and excluded this subject, it does not appear that this subject's comparatively greater feelings of depression at the time of testing confounded the results of this study.

Hypothesis 15

It was assumed that many of the FM subjects included in this study would be taking antidepressant medications. Sedating antidepressants were hypothesized to negatively affect cognitive functioning, whereas nonsedating antidepressants were not expected to have this effect. In the current study, several of the FM subjects were taking sedating antidepressants and/or nonsedating antidepressants. In the three-group depression ANOVA described above, the nondepressed FM group, but not the depressed FM group, scored significantly worse than controls on the ACTMN3. It was possible that antidepressant medications within the nondepressed FM group could have affected performance on this measure. Also, these medications could have affected performance in the FMD group, who performed significantly worse as compared to controls on the animal-naming task. Further complicating these findings was the fact that three of the FM subjects had taken an opioid on the day of testing, which also could have affected cognitive performance. Given the possible interaction of all four of these factors, it would have been ideal to have analyzed the effects of the presence or absence of depression, opioid medication, sedating antidepressants, and nonsedating antidepressants on cognitive functioning in FM using a 2X2X2X2 factorial model. However, subjects did not fall into all of the 16 possible conditions required to carry out such an analysis. Thus, in order to attempt to control for the effects of depression and opioid medication while investigating the possible effects of antidepressant medication on cognition, a two-way ANOVA was conducted on a selected subgroup of FM subjects who were not depressed according to DSM-IV criteria. One subject in this group had taken an opioid on the day of testing, and thus, this subject was excluded from the analysis. All necessary levels for carrying out this analysis within the nondepressed, but not the depressed FM subjects, were represented. Two variables for each of the three cognitive domains, all of which could be analyzed parametrically, were chosen to act as dependent measures in the analyses.

Means and standard deviations for each of the four groups of subjects are listed in Table 22. Using an alpha level of .05, a two-way ANOVA for ANIMALS demonstrated no significant sedating antidepressant by nonsedating antidepressant interaction [F(1) = .26, p = .619], no significant main effect for sedating antidepressant [F(1) = 3.82, p = .074], and no significant main effect for nonsedating antidepressant [F(1) = 2.15, p = .168]. A two-way ANOVA for LETTER C similarly resulted in no significant sedating antidepressant by nonsedating antidepressant interaction [F(1) = .42, p = .530] and no significant main effect for sedating antidepressant [F(1) = .00, p = .988]. However, a significant main effect was found for nonsedating antidepressant [F(1) = 15.89, p = .002]. This effect is displayed in Figure 2. Pairwise, Bonferroni adjusted comparisons demonstrated that subjects who took both a sedating and a nonsedating antidepressant performed significantly worse on this test than those who took a sedating antidepressant only (p = .032). Also, subjects who took both sedating and non sedating antidepressants scored significantly worse than subjects who took no medication (p = .026). Thus, on one of the language measures, nonsedating antidepressants appeared to negatively affect performance in nondepressed, opioid-free FM subjects.

Table 22

Means and Standard Deviations for the Four Levels of Presence or Absence of Sedating and Nonsedating Medications Among Nondepressed, Opioid-free FM Subjects

Variable	Sed + Nonsed[a]	Sed Only[b]	Nonsed Only[c]	No Med[d]	Bonferroni*
ANIMALS	14.03(3.7)	15.7(3.2)	16.52(2.1)	21.6(5.3)	None
LETTER C	9.0(1.4)	16.3(1.7)	10.0(2.0)	15.3(1.1)	Sed + Nonsed < Sed Only Sed + Nonsed < No Med
PASATMN4	66.0(8.5)	59.4(9.8)	78.8(12.0)	66.9(6.4)	None
ACTMN3	48.8(4.9)	50.4(5.6)	59.8(6.9)	72.3(3.7)	Sed + Nonsed < No Med Sed Only < No Med
ROCFDELAY	8.5(1.7)	8.7(2.0)	12.0(2.5)	9.1(1.3)	None
CVLT1-5	58.3(5.8)	44.3(3.5)	60.5(12.0)	58.9(12.9)	None

Note. ANIMALS = number of animals generated; LETTER C = number of words beginning with the letter 'c' generated; PASATMN4 = mean of the four trial scores of the PASAT; ACTMN3 = mean of the three trial scores of the ACT; ROCFDELAY = delay trial score of the ROCF; CVLT1-5 = total number correct for the five learning trials of the CVLT; Sed + Nonsed = FM subjects taking both sedating and nonsedating antidepressant medication; Sed Only = subjects taking sedating antidepressant medication only; Nonsed Only = subjects taking nonsedating antidepressant only; No Med = subjects taking no medication.
[a] $n = 4$; [b] $n = 3$; [c] $n = 2$; [d] $n = 7$.
*$p < .05$.

On Letter C, the group on both sedating and nonsedating antidepressant medication scored 5.7 standard deviations below the medication-free group. This group was impaired according to norms provided by Benton & Hamsher (as cited in Lezak, 1995). Also, the group on nonsedating medication scored 4.8 standard deviations below the medication-free group. However, this group's score was not considered clinically impaired according to normative data (Benton & Hamsher, as cited in Lezak, 1995). Thus, the Sedating + Nonsedating group appeared to be most impaired on Letter C performance.

For the attentional measures, a two-way ANOVA conducted on the mean percent correct of the four trials of the PASAT demonstrated no significant sedating antidepressant by nonsedating antidepressant interaction [$F(1) = .08$, $p = .783$], no significant main effect for sedating

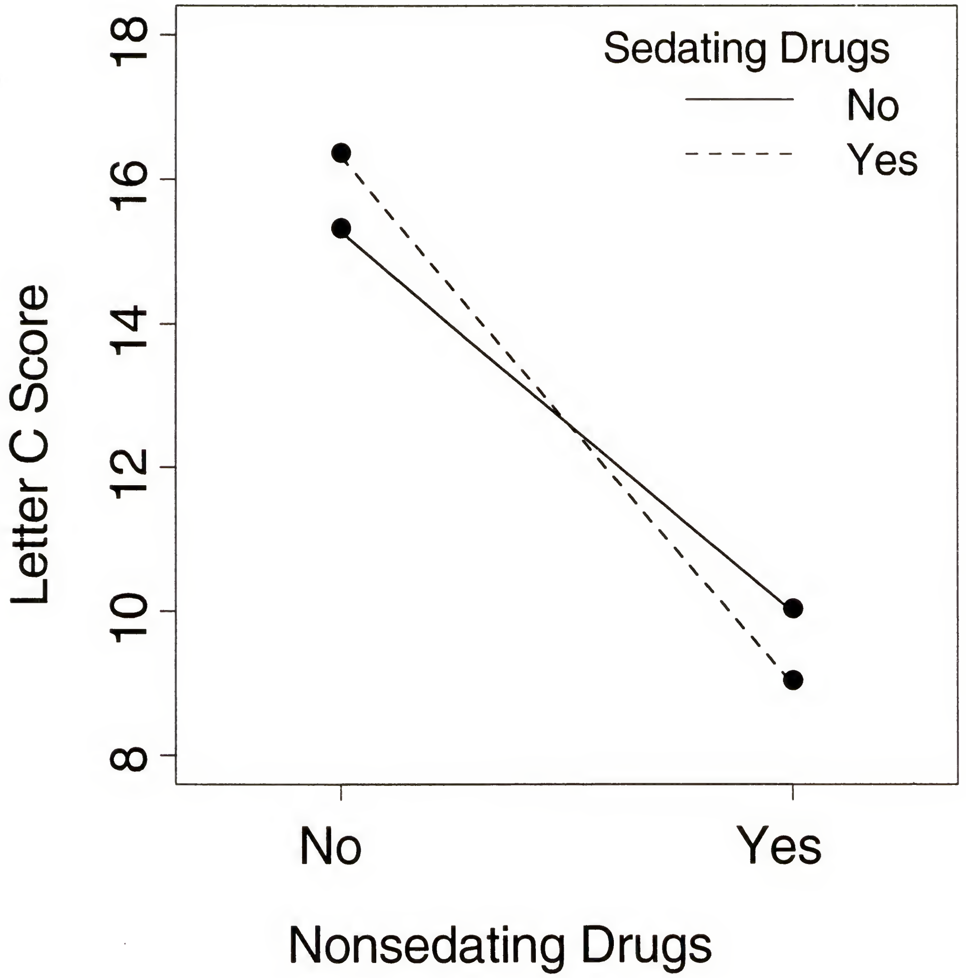

Figure 2. Main Effect of Nonsedating Antidepressant Medication on Letter C Performance in Nondepressed, Opiod-Free FM Subjects

antidepressant [F(1) = 1.15, p = .306], and no significant main effect for nonsedating antidepressant [F(1) = .96, p = .347]. Upon analysis of the mean percent correct for the ACT, no significant sedating antidepressant by nonsedating antidepressant interaction was found [F(1) = 1.02, p = .332], and no significant main effect for nonsedating antidepressant was demonstrated [F(1) = 1.72, p = .214]. However, a significant main effect for sedating antidepressant was found [F(1) = 9.33, p = .010]. This effect can be seen in Figure 3. Bonferroni adjusted post-hoc comparisons demonstrated that subjects on both a sedating and a nonsedating antidepressant scored significantly poorer than those on no medication (p = .014), and those subjects on a sedating medication only also performed significantly worse than medication-free subjects (p = .041). Thus, on one of the attentional measures (ACT), sedating antidepressants appeared to negatively affect performance among the nondepressed, opioid-free FM patients.

Subjects on both sedating and nonsedating medication scored 6.4 standard deviations below subjects taking no medication on the ACTMN3. Also, subjects who were taking sedating medication only scored 5.9 standard deviations below the medication-free group. Thus, the two medication groups scored substantially lower than the medication-free groups on this measure.

A two-way ANOVA done on the memory measures found that, for ROCFDELAY, there was no significant sedating antidepressant by nonsedating antidepressant interaction [F(1) = .61, p = .450], no significant main effect for sedating antidepressant [F(1) = 1.06, p = .324], and no significant main effect for nonsedating antidepressant [F(1) = .48, p = .500]. For the CVLT1to5, there also was no sedating significant antidepressant by nonsedating antidepressant interaction [F(1) = 1.08, p = .319], no significant main effect for sedating antidepressant [F(1) = 1.06, p = 2.36], and no significant main effect for nonsedating antidepressant [F(1) = 1.81, p = .203]. Thus, there appeared to be no effect of antidepressant medication on these measures of memory functioning among nondepressed, opioid-free FM subjects.

Thus, the hypothesis that sedating antidepressants would affect attention, memory, and learning abilities was partially confirmed in that these medications were found to negatively affect the ACT, which is a measure of attention and memory. However, sedating antidepressants

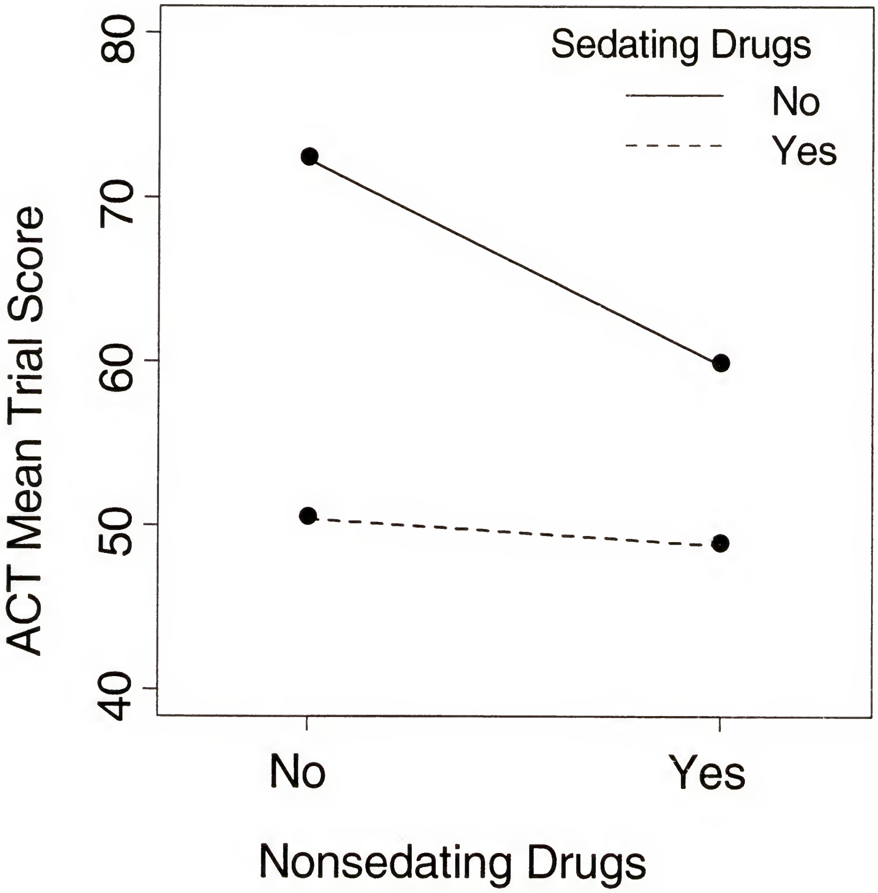

Figure 3. Main Effect of Sedating Antidepressants on ACTMN3 Performance in Nondepressed, Opioid-Free FM Subjects.

did not appear to negatively affect learning abilities as measures by the CVLT1-5. Nonsedating antidepressants were demonstrated to negatively affect letter fluency, a finding that was unexpected.

Comparison of Depression-free and Medication-free FM Subjects Versus Controls

A small subgroup of FM subjects ($n = 7$) were neither depressed nor on any type of medication. Thus, it was of interest to compare this subgroup's performance with controls to determine if "pure" FM subjects were impaired on cognitive testing. One-tailed t-tests (and Mann Whitney U tests, when appropriate) were conducted comparing performance on several of the language, attentional, and memory measures. Analyses of the ANIMALS and CVLT1-5 were conducted on the transformed variables. The results of these analyses are presented in Tables 23, 24, and 25. None of these comparisons were significant following Bonferroni adjustment. Thus, there was no evidence to suggest that FM subjects who were free of depression and medication performed significantly worse on cognitive testing than controls. Also, on measures for which there are published norms, neither the FM group nor the controls scored less than one standard deviation below this norm, suggesting that neither group was clinically impaired on these measures.

Effect of Duration of Antidepressant Medication Usage on Cognitive Abilities in FM

To determine if the length of time on an antidepressant medication was related to cognitive performance among FM subjects using these medications, Pearson correlations (or Spearman Rank correlations, when appropriate) were conducted. Length of time on sedating antidepressant was correlated with these subjects' scores on representative language variables (ANIMALS, BNT, LETTER C), attentional measures (ACTMN3, PASATMN4), and memory measures (CVLT1-5, PERCATOB, PRLDFR, ROCFDELAY). Length of time on nonsedating antidepressant was similarly analyzed. Neither the length of time on a sedating medication or the length of time on a nonsedating medication correlated significantly (at an alpha level of .05) with any of these cognitive variables. Thus, there was no evidence to suggest that cognitive functioning in FM subjects correlates significantly with duration of antidepressant medication usage.

Table 23

Parametric Comparison of Nondepressed, Medication-Free FM Subjects and Controls

Variable	FM Group[a]	Normative Group[b]	t[c]	1-tailed p
LETTER C	15(3.3)	14(5.4)	.464	.323
ANIMALS	19.4(2.8)	20.5(5.9)	-.181	.429
ROCFIMM	9.6(3.7)	9.0(3.0)	.394	.349
ROCFDELAY	9.1(4.0)	8.9(3.4)	.177	.431
PASAT4	43(14.3)	57.3(18.4)	-1.89	.035
ACT18	69.4(16.8)	61.3(20.3)	.964	.172
CVLT1-5	55.9(13.6)	56.2(10.5)	-.040	.484
PERCHANGE A to B	3.6(24.1)	-14.9(23.8)	1.80	.041

Note. Scores are listed as means (standard deviations in parentheses); LETTER C = number of words beginning with the letter 'c' generated; ANIMALS = number of animals generated; ROCFIMM = immediate recall trial of the Rey Osterrieth Complex Figure; ROCFDELY = delayed recall trial of the ROCF; PASAT4 = percent correct on the fourth trial of the Paced Auditory Serial Addition Task; ACT18 = percent correct on the 18-second delay trial of the Auditory Consonant Trigrams test; CVLT1-5 = total number correct for the five learning trials of the California Verbal Learning Test; PERCHANGE A to B = percent of items recalled on trial B as compared to Trial A.

[a]n = 7. [b]n = 24.

[c]df = 29.

Table 24

Parametric Comparison of Nondepressed, Medication-Free FM Subjects and Controls

Variable	FM Group Mean	Control Group Mean
BNT	57.6(1.6)	55.1(4.0)
PRLDFR	81.00(22.4)	85.3(13.6)

Note. Scores listed as means (standard deviations in parentheses); BNT = Boston Naming Test; PRLDFR = percent of originally learned items recalled on long delay free recall trial of the California Verbal Learning Test.

[a]n = 7. [b]n = 24.

Table 25

Nonparametric Comparison of Nondepressed, Medication-free FM Subjects and Controls

Variable	FM Mean Rank	Control Mean Rank	Mann Whitney U[a]	1-Tailed p
BNT	21.14	14.50	48.00	.043
PRLDFR	15.72	16.08	82.00	.462

Note. BNT = Boston Naming Test; PHONCUE = number of times subject required cueing on the BNT; BNTPROP = proportion of times subject benefited from cueing on the BNT; ANIMALS PERS = number of perseverations on Animals; LET C PERSEV = number of perseverations on Letter C.
[a] $n = 31$.

Effects of FM Symptomatology on Cognitive Functioning

Hypothesis 16

Because pain and fatigue have both been found to negatively affect attentional abilities, it was expected that pain and fatigue levels in the FM group would negatively correlate with scores the attentional tests. It was also thought that pain and fatigue would negatively affect other cognitive abilities. Pain and fatigue ratings for the month prior to testing (derived from SF-36 subtests: Bodily Pain and Vitality scales) and "time of testing" ratings (derived from visual analogue scales: VASFAT, VASMAL, VASPAIN, and from dolorimeter testing: DOLMEAN) were correlated with language, attentional, and memory measures using one-tailed Pearson correlations (or one-tailed Spearman Rank correlations, when appropriate). However, no significant correlations were found between any of the pain or fatigue ratings and the language measures (BNT, ANIMALS, LETTER C), attentional measures (PASATMN, ACTMN), or memory measures (CVLT1, CVLT1-5, PERCATOB, or PRLDFR) using an alpha level of .01. For the pain correlations, Pearson and Spearman Rank correlation coefficients ranged from -.021 to .343, with significance levels ranging from .479 to .050. Here, there was a trend towards a significant relationship between lower scores on the mean ACT scores and a lower pain tolerance as measured by dolorimeter testing (r = .343, p = .05). For the fatigue correlations, Pearson and Spearman Rank correlation coefficients ranged from -.157 to -.470, with significance levels ranging from .212 to .010. Here, there was a trend towards a significant relationship between lower VASFAT scores, which measured level of fatigue at the time of testing, and lower mean PASAT scores (r = -.470; p = .010). Thus, there was not significant evidence to support the hypothesis that pain and fatigue correlated with performance on cognitive measures. However, there was a trend towards a relationship between level of pain and fatigue and performance on the attentional measures.

Hypothesis 17

It was also hypothesized that severity of illness among FM subjects would correlate negatively with cognitive performance. This hypothesis was tested by conducting one-tailed Pearson correlations (or Spearman Rank correlations, when appropriate). Two severity of illness scores (SF-36 mean score and VAS mean score) were correlated with language measures (BNT, ANIMALS, LETTER C), attentional measures (PASATMN4, ACTMN3), and memory measures (CVLT1, CVLT1-5, PERCATOB, or PRLDFR). No significant correlations were found among any of these variables using an alpha level of .01. For the SF-36 means score correlations, Pearson and Spearman Rank correlation coefficients ranged from .062 to .366, with significance levels ranging from .387 to .039. Here, there was a trend towards a significant relationship between better performance on the BNT and a lower level of severity of illness, as measured by the SF-36 (rho = .366, p = .039). For the VAS mean score correlations, Pearson and Spearman's rho coefficients ranged from -.005 to -.181, with significance levels ranging from .490 to .199. Thus, there was no evidence to suggest that severity of illness level was significantly related to performance on cognitive testing. However, there was a trend towards a significant relationship between severity of illness and performance on the BNT.

Comparison of Hospital-Recruited versus Community-Recruited FM Subjects

To determine whether or not differences in cognitive functioning occurred on the basis of recruitment source, two-tailed t-tests (or Mann Whitney U tests, if appropriate) were used to compare subjects recruited from the hospital versus from the community on all of the intellectual, language, memory, and attentional measures. This analysis was conducted because subjects recruited from the hospital were characterized as being more severely ill, having more severe chronic pain, and experiencing more emotional problems that interfered with daily functioning than community subjects according to the earlier analysis that compared these two groups on the SF-36. No significant differences were found between the groups at an alpha level of .05. Thus, it does not appear that source of recruitment differentially affected the performance of FM subjects in the current study.

Examination of the Effect of Order of Test Administration on Cognitive Performance

Tests used in the current study were administered in a counterbalanced design in which odd-numbered FM and control subjects completed the first half of the tests first, and even-numbered subjects completed the second half of the tests first. This allowed for evaluation of whether or not performance on the cognitive tests declined differentially between the two groups over the course of the testing session. To do this, a two-way analysis was conducted to explore the possibility of an interaction between time of administration (early versus late) and group (FM versus control). An interaction would have implied that FM subjects performed differently than controls on the cognitive measures depending on whether or not they had received a test early versus late, suggesting that some process incurred during the testing session, such as fatigue or pain, had differentially affected the groups. The two-way ANOVA was conducted on one of the language variables (ANIMALS), one of the memory measures (CVLT1-5), and two of the attentional measures (PASATMN4 and ACTMN3).

No group by time interaction was found for ANIMALS [F (1) = 2.27, p = .139], and no time main effect was found [F (1) = .40, p = .530]. A group main effect was found [F (1) = 5.81, p = .020], as would be expected in that group differences had been found during earlier analyses between the groups' scores on this measure. For PASATMN4, no group by time interaction was found [F (1) = .83, p = .367], no time main effect was found [F (1) = 2.51, p = .120], and no group main effect was found [F (1) = 1.74, p = .194]. For ACTMN3, no group by time interaction was found [F (1) = .13, p = .721]. However, a time main effect was found [F (1) = 6.53, p = .014], indicating that both groups performed worse on this measure when receiving it later rather than earlier in the testing session. Also, a group main effect was found [F (1) = 4.68, p = .036]. These effects can be seen in Figure 4. Finally, for the CVLT1-5, no group by time interaction was found [F (1) = 0.00, p = .948], no time main effect was found [F (1) = 2.93, p = .094], and no group main effect was found [F (1) = .02, p = .896]. Thus, these analyses demonstrated that, because no group by time interactions were found, there was no evidence to suggest a differential degradation in performance between the two groups across the testing session.

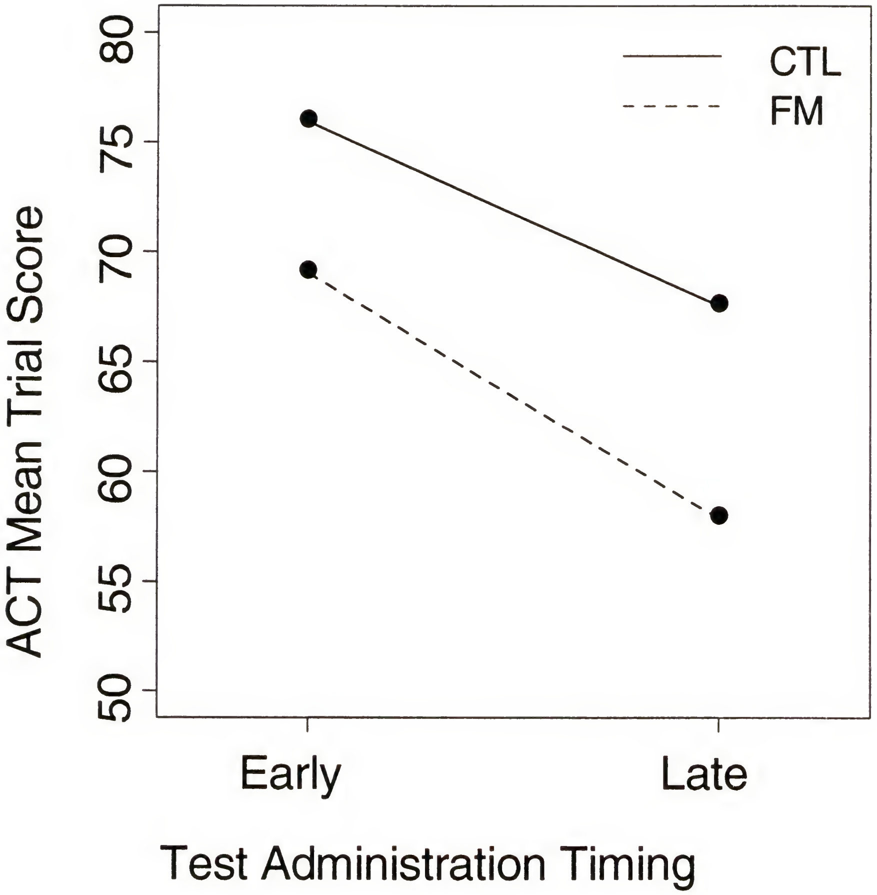

Figure 4. Main Effect of Time and Group on the ACT for FM and Control Subjects

CHAPTER 4
DISCUSSION

The primary aim of the current study was to investigate whether or not cognitive deficits exist among individuals with fibromyalgia. It was also of importance to make methodological improvements over previous studies of cognitive functioning in FM. To do this, the current study employed a larger sample of FM subjects and provided better documentation of the criteria used to diagnose the disorder. Also, the role of the effects of medication on cognition in FM was investigated for the first time. Additionally, better care was taken in accurately assessing level of depression by using a measure that did not contain confounding somatic items. This was done to allow more accurate measurement of the relationship between depression and cognitive performance in FM. Finally, several measures of severity of illness were employed, allowing for investigation of the relationship between severity of illness and level of depression and between severity of illness and performance on cognitive measures, neither of which had been explored in earlier studies. In this section, a discussion of the results found in the current study will be presented along with a critique of whether or not the primary aims of the study were met.

Descriptive Findings

Clinical Utility of Control Points in the Diagnosis of FM

In the current study, FM subjects presented with only a one-kilogram difference in mean pain threshold levels between control and tender points on dolorimeter testing. Also, means for both control and tender points were positive (meaning that the points were rated as "painful" by the subject at, or below, four-kilograms of pressure). Other studies have also reported a high incidence of positive control points among FM patients. For example, Wolfe (1998) found that

63% of a FM sample had positive control points. The occurrence of positive control points has been informally used by some examiners to distinguish between patients who have FM versus a psychogenic condition (Wolfe, 1997). However, based on his results, Wolfe (1998) suggested that control point positivity should no be used to disqualify a diagnosis of FM.

Okifuji, Turk, Sinclair, Starz, and Marcus (1997) have reported that the traditional procedure of designating a point as positive (based on the patient's dichotomous "painful" versus "non-painful" rating) is not as sensitive as is asking the subject to rate pain level on a continuous scale. These authors reported that using the continuous rating scale (with a cut-off of 2 on a scale of 0-10 designating a positive point) was more sensitive and specific than the dichotic method in differentiating between FM and chronic headache patients. Also, with this method, a highly significant difference was found between pain ratings for tender versus control points in FM subjects. Thus, it appears that if control points are to be used in the differential diagnosis of FM, a continuous pain rating scale is more effective than the traditional method in determining whether or not these points are positive.

Depression and Anxiety in FM

In the current study, FM subjects were found to be significantly more depressed and anxious than controls on the basis of the POMS (McNair et al., 1992) Anxiety and Depression scores. This finding was expected because the control group had been screened for psychiatric illness. However, this did not allow for a comparison of depression and anxiety levels between FM subjects and the general population. Unfortunately, age-appropriate POMS norms were not available in the manual for women in the general population. FM subjects were also compared to norms from a medically ill sample, although the age range of this group was not specified. Here, the FM group was found to be more depressed and anxious than the normative medical group. However, the majority of the normative group was made up of individuals having an unspecified medical condition, who may not have been chronically ill. Thus, because more appropriate POMS norms were not available, neither of these comparisons provided information as to how the current FM sample compared to the general population or to patients having an equal level of impairment.

Neuropsychological Findings

Language Functioning in FM

When the FM group was compared to controls, no deficit was found in confrontational naming, nor did FM subjects appear to benefit from phonemic cueing more than controls on this measure. Thus, it does not appear that FM subjects have difficulty with retrieval of names of objects from memory. FM subjects also appeared to perform normally on letter and animal fluency, which were given because less of a ceiling effect is likely to occur in these measures as opposed to the BNT. Here, the mean scores of the FM group were not in the impaired range. However, according to norms in Spreen and Strauss (1998), 58% of the FM group and only 20% of the control group performed in the impaired range on animal fluency measure. Thus, a subgroup of FM subjects was impaired on this measure.

When the effects of antidepressant medication on language were explored, deficits were noted in letter fluency. For example, a main effect for nonsedating antidepressants was found among nondepressed FM subjects on the number of words produced to the letter “c”. This group produced only 10 words per minute. FM subjects who were on both nonsedating and sedating antidepressants were even more impaired, generating only 9 words per minute. There appear to be no studies that have investigated the effects of these nonsedating antidepressants on language functioning. Thus, it is unclear why this effect was found.

Alternatively, the use of nonsedating antidepressants may not have caused these deficits. It is possible that this analysis was affected by the distribution of various types of sedating antidepressants across the groups and by the small number of subjects available for the analysis.

For example, Table 22 showed that the most impaired group on Letter C was the Sedating + Nonsedating group, which performed significantly worse than both the Sedating group and the Medication-free groups. However, three out of four of the subjects in the Sedating + Nonsedating group were taking Elavil, which has been found to be more sedating and to cause more impairment in attention and verbal recall than any of the other sedating antidepressants (Amado-Boccara et al., 1995). In contrast, none of the subjects in the Sedating group were taking Elavil. This may explain why the Sedating + Non-sedating group performed worse than the Sedating group. The Non-sedating group did not perform significantly worse than the Medication-free group, although their scores were substantially lower than the Medication-free group. However, only two subjects fell into the Non-sedating group, and thus, this group was not well represented. Therefore, this analysis may have been confounded by variations in the type of sedating medications used and in the number of subjects across groups. Overall, it appears that antidepressants may adversely affect letter fluency. Whether or not this effect is caused by sedating or nonsedating antidepressants is uncertain. Because no effect of medication was found on animal naming performance, deficits in letter fluency may have been due to the frontal nature of the latter task. It is possible that deficits in letter fluency reflected difficulties with self-generation of a strategy by which to organize the search of words.

No evidence was found to suggest a significant relationship between duration of sedating or nonsedating antidepressant medication usage and language functioning in FM. Thus, it appears that FM patients are able to use these medications over a prolonged period of time without experiencing a progressive decline in language abilities.

It is important to note that some other factor besides medication use may have affected cognitive performance in these groups. Differences could not be explained by depression status because only nondepressed subjects were used in this analysis. An analysis of possible differences in pain level among the four medication groups as measured by dolorimeter testing was not significant, suggesting that pain could not account for this finding. Thus, medication may be responsible for the deficits noted.

The effect of depression on language functioning based on DSM-IV diagnosis was also investigated. Here, depressed FM subjects were mildly impaired (and performed significantly worse than control subjects) on ANIMALS, whereas nondepressed FM subjects were not. Because the possible effect of medication on animal fluency could not be investigated among depressed FM subjects, it was not possible to determine if this impairment was caused by depression or by medication.

No significant relationship was found between anxiety as measured by the POMS and any of the language measures. Also, no significant relationship was found between any of the prominent symptoms of FM (pain, fatigue, malaise) and performance on language testing, or between severity of illness and language abilities.

Perhaps the most informative analysis demonstrated no significant differences between nondepressed, nonmedicated FM subjects and controls among any of the language variables. Here, both groups performed within the normal range on these measures. Thus, it appears that nothing within the disease process itself causes impaired language functioning in FM. FM patients who complain of word-finding difficulty may be those who are taking anti-depressant medication.

Attentional Functioning in FM

On the attentional measures, a significant group difference was found for the ACT, on which the total FM sample was mildly clinically impaired. When the effects of depression were examined, the nondepressed FM group, but not the depressed FM subjects, performed significantly worse than controls. The nondepressed subgroup was clinically impaired on the ACT. When the influence of medication on test performance in this subgroup was analyzed, a significant effect for sedating antidepressants was found. Here, both the Sedating + Nonsedating FM group and the Sedating FM group performed significantly worse than the medication-free FM group. This finding is consistent with previous reports of sedating antidepressants adversely affecting attentional abilities and memory (Amado-Boccara et al., 1995). Thus, it appears that complaints of attentional/memory difficulties in FM may be due to sedating medication effects. Length of time on a sedating antidepressant did not correlate with performance on this measure, suggesting that cognitive functioning does not become progressively impaired as duration of drug usage increases.

No group effects were found between the entire FM sample and controls on the PASAT. There also were no differences among depressed FM, nondepressed FM, and control subjects on this measure. Finally, there appeared to be no effect of medication use on the PASAT.

Differences between the FM sample and controls may have been found on the ACT but not the PASAT because there is more of a distraction component to the ACT. The PASAT requires sustained attention and the ability to hold information in memory while manipulating the information (working memory) but involves much less distraction. However, the ACT requires the ability to recall briefly presented information after the subject has engaged in a highly distracting activity (counting backwards by 3's) for as long as 18 seconds. The purpose of this distraction is to prevent rehearsal of the consonants. The findings of the current study may reflect the fact that FM patients are more vulnerable to loss of information than are normal controls when active distraction prevents rehearsal.

A strong trend was found between level of fatigue at the time of testing and performance on the PASAT ($\underline{p} = .02$), but not the ACT. It is possible that this occurred because the PASAT requires sustained attention over a longer period of time and, overall, requires greater effort than the ACT. Other symptoms associated with FM, including levels of pain, severity of illness, and anxiety correlated with neither the PASAT nor the ACT. Thus, although pain and anxiety have been associated with poorer performance on attentional measures, this did not occur among FM subjects in the current study.

When depression- and medication-free FM subjects were compared to controls, no significant differences were found for either of the attentional measures. Thus, it appears that a subgroup of patients with FM, possibly those who are taking sedating antidepressant medication, have greater difficulty learning information when distracted. However, there appears to be no effect of the disease process itself on attentional abilities in FM.

Memory Functioning in FM

No differences were found between FM subjects and controls on any of the memory tests, nor were any of the FM scores on these measures in the clinically impaired range. Thus, the FM group displayed no difficulties with recall of remote information as measured by the Information subtest of the WAIS-R. They also appeared to benefit from cueing on this measure no more often than controls, further suggesting normal recall abilities. They performed normally on the first trial of the CVLT, indicating normal immediate memory abilities, and were able to learn as much verbal information as controls across the five trials of this measure, suggesting normal learning abilities. The FM group displayed an effective learning strategy in that they used semantic clustering as frequently as controls. Also, they were no more susceptible to proactive or retroactive interference than controls. The FM group was able to recall as much information as controls after a long delay. Finally, FM subjects did not perform better on the recognition trial as compared to recall trials, which would have suggested possible difficulties with recall of verbal information. Thus, it does not appear that FM subjects have impaired verbal recall when no form of distraction is present to prevent rehearsal of the information.

No differences were found between controls and the FM group on a measure of immediate and delayed visual information, the ROCF. Thus, it appears that visual memory is not impaired in FM. However, no visual memory measure that included a distracting task was used in the current study. Thus, it is possible that the pattern of performance found in verbal memory functioning may have been demonstrated in visual memory functioning if a distracting task had been used.

No significant correlations were found in FM subjects between performance on memory measures and levels of depression, anxiety, severity of illness, or symptomatology. Also, no differences were found among depressed FM subjects, nondepressed FM subjects, and controls. Finally, there appeared to be no effect of antidepressant medication on these measures.

Results of the Current Study as Compared to Previous Findings

In a previous study on cognitive functioning in FM (Landro et al., 1997), letter fluency was significantly worse in FM than healthy control subjects, but the mean score for the FM group was not clinically impaired. Unfortunately, the authors did not report the percentage of subjects in the FM and control groups that performed in the impaired range. In the current study, letter fluency was not significantly worse in the entire FM sample as compared to controls, but the subgroup of subjects taking both sedating and nonsedating antidepressants were clinically impaired and significantly worse than controls on the measure. This, together with the finding of normal letter fluency in the nondepressed and unmedicated FM subgroup, suggests that the Landro et al. (1997) results may have been caused by a medication effect.

The Sletvold et al. (1995) study found attentional deficits on one trial of the PASAT and the Trail Making Test. In the current study, in which the entire PASAT was administered, no differences were found between controls and the FM group. Because the entire PASAT was not administered in the standard manner in Sletvold et al., it is possible that this finding was not representative of FM subjects' true abilities. However, there was a trend towards a significant relationship in the current study between fatigue and PASAT performance. Thus, it is possible that subjects in the Sletvold et al. study were more fatigued than those used in the current study. The authors apparently did not investigate the relationship between their measure of fatigue and PASAT scores.

The Kaplan et al. (1992) study found mildly impaired verbal memory on the Logical Memory subtest (but not on the CVLT), and Landro et al. (1997) found significant differences between FM subjects and controls on two memory measures, the Randt Memory and the Code

Memory tests. However, no impairment was found in verbal or visual memory in the current study. Also, neither depression nor medication appeared to affect memory abilities among FM subjects. However, because of small sample size in the medication analysis and because the depression analyses were confounded by medication use, it is possible that such effects may have gone undetected. Perhaps most importantly, no differences were found between nondepressed, medication-free FM subjects and controls in memory abilities in the current study, suggesting there is no apparent affect from the disease process involved in FM that causes memory impairment. This type of analysis has not been conducted in previous studies, and thus, impaired performance in these studies may have been due to medication use or depression. Future studies using larger sample sizes will be necessary to clarify these inconsistencies.

Limitations of the Current Study

In order to determine if adequate sample sizes were used in the current study, power calculations were conducted using STPLAN. For a two-group, two-tailed t-test, a sample of 24 subjects in each group was adequate to detect a one standard deviation difference between the groups with 92% power. For a one-tailed t-test, this size sample was adequate to detect a one standard deviation difference with 96% power. With sample sizes of 7 and 24 (as was used in the comparison between nondepressed, medication-free FM subjects and controls), it was possible to detect a 1.25 standard deviation difference between the group means with 80% power using a one-tailed t-test.

For the correlational analyses, it was possible to detect a one-tailed correlation of .50 with 80% power using a sample of 24. For a nondirectional correlation, it was possible to detect a correlation of .55 with 80% power and a sample size of 24. Thus, for the basic pairwise comparisons done in the current study, the sample size appears to have been adequate. However, it is not likely that an adequate sample size was used in the subgroup analyses of the effects of medication on cognition in FM. Here, results suggested that medication may affect language and attentional abilities, but it was not clear whether the results were caused by sedating antidepressants, nonsedating antidepressants, or an interaction of these two variables. Thus, this issue remains unsolved due to inadequate sample size.

An additional limitation to the current study was that no subjects could be found who were depressed and medication-free. Thus, valid analysis of the effects of depression on cognition in FM (without the possible confounding effect of medication) could not be conducted.

The fact that DSM-IV diagnostic criteria were used to divide the FM group into depressed/nondepressed groups may have also limited the results of the current study. Because this method of diagnosis tends to overestimate depression in chronic pain populations, it is possible that there were subjects within the depressed FM group who were not actually depressed, even though care was taken to accurately diagnose these subjects. However, no established cut-off exists for the POMS Depression scale above which subjects are classified as being depressed, so the DSM-IV criteria had to be used for this analysis. Because of this, it is possible that a lack of differences were found in cognitive functioning between depressed and nondepressed subjects because they had been incorrectly classified. Thus, this issue cannot be clarified until a measure of depression becomes available that does not overestimate depression and has an established cut-off above which clinical depression is diagnosed.

Finally, because multiple comparisons were conducted, it is possible that Type I errors were committed, leading to spurious findings. However, a conservative form of correction for these errors, the Bonferroni adjustment, was used to help prevent erroneous rejection of the null hypotheses. In spite of this, it is possible that the few significant results reported in this study were actually spurious.

Future Directions for Research on Cognition in FM

The effect of FM on cognition is a relatively new area of research, with only a few studies on this topic having been published thus far. Although not all of the aims of the current study were met, new information on cognitive functioning in FM was revealed. However, more studies need to be conducted in order to clarify these results. Of most importance would be to conduct a study using a larger sample of subjects such that proper analysis of cognition in subgroups of FM subjects could be carried out. Specifically, it would be important to include subjects who represented each of the possible combinations of the presence or absence of depression, sedating antidepressant medication, nonsedating antidepressant medication, and pain medication. It would be especially informative to include subjects who are depressed but not medicated.

Given the trend in the current study towards a relationship between fatigue and performance on the PASAT, it would be interesting to examine PASAT performance in FM subjects using a control group of sleep deprived normal controls. It would also be of interest to compare the performance of FM subjects who were at their best at the time of testing (as they were in the current study) with FM subjects when they were not at their best. This might find that cognitive deficits are more apparent in FM subjects when they are, for example, more fatigued.

It might also be informative to use the Code Memory Test, which is a visual memory task that involves a distraction component, to investigate the possible relationship between performance on this type of test and medication use in FM. When used previously by Landro et al. (1998), differences were found between FM and control subjects on this measure, but the possible role of antidepressant medication use in FM performance was not investigated. Given the current finding that medication use may have impeded performance on a verbal memory/distraction task, medication might also be expected to have a similar affect on nonverbal memory when distraction is present.

Given the fact that measurement of control points was not clinical meaningful in the current study, it may be unnecessary to measure pain threshold at control points in future studies. However, if the method proposed by Okifuji et al. (1997) is used, measurement of these points may be more meaningful.

Finally, it would be helpful for studies to begin including a severity of illness measure, such as the SF-36 Health Survey (Ware, 1993). This would allow for further investigation of the possible relationship between levels of depression and severity of illness in FM.

APPENDIX A
SUBJECT SCREENING FORM

Subject # ______

(Fibromyalgia Subjects)

1. Age. ________ (must be between ages 21 and 60 to participate)

2. Education level. ____________ (must have at least a 7th grade education level to participate)

3. Does subject have concomitant rheumatic or other medical illness in addition to FM? ___________ (if yes, cannot participate)

4. Does subject have chronic pain due to condition other than FM? _________ (if yes, cannot participate)

5. Does subject have a current psychiatric diagnosis? ______ If yes, what? ____________ (if has current diagnosis other than depression or anxiety disorder, cannot participate)

6. Has subject been diagnosed with depression in the past? __________

7. Has subject experienced a head injury with loss of consciousness? __________ (if yes, cannot participate)

8. Has drug use in the past ever interfered with your social, family, or occupational functioning or is it currently interfering with these things?_________ (if yes, cannot participate)

9. Dolorimeter score - number of tender points at which subject reports pain using dolorimeter at 4 kg pressure. __________

   Meets ACR criteria for FM? (11 tender points) __________(if no, cannot participate)

10. Did subject grow up in the United States? _________ (if no, cannot participate)

11. Do you currently drink alcohol? ______ How much per week? _________ Have you drunk alcohol in the past?______How much per week?_________ (Unless person has never drunk alcohol, give CAGE)

12. "CAGE" exam:
    Have you ever felt you should Cut down on your drinking?____
    Have people ever Annoyed you by criticizing your drinking?____
    Have you ever felt bad or Guilty about your drinking?____
    Have you ever had a drink first thing in the morning to steady your nerves or get rid of a hangover? (Eye-opener) ____
    (if yes to any of above, cannot participate)

APPENDIX B
SUBJECT SCREENING FORM

Subject #______

(Healthy Control Subjects)

1. Age. ________ (must be between ages 21 and 60 to participate)

2. Education level. ____________ (must have at least a 7th grade education level to participate)

3. Does subject have a rheumatic or other medical illness?________________________ (if yes, cannot participate)

4. Does subject have chronic pain? _________ (if yes, cannot participate)

5. Does subject have a current or previous psychiatric diagnosis? ___________ (if yes, cannot participate)

6. Has subject experienced a head injury with loss of consciousness? __________ (if yes, cannot participate)

7. Has drug use in the past ever interfered with your social, family, or occupational functioning or is it currently interfering with these things?_________ (if yes, cannot participate)

8. Is subject currently taking any medication(s)? ________
   If yes, what medication(s)? _________________________________
   (inquire what medication is for, and make sure that it is not to treat any of the above exclusionary conditions)

9. Did subject grow up in the United States? _________ (if no, cannot participate)

10. Do you currently drink alcohol? ______ How much per week? _________ Have you drunk alcohol in the past?______ How much per week?_________
    (Unless person has never drunk alcohol, give CAGE)

11. "CAGE" exam:
    Have you ever felt you should Cut down on your drinking?____
    Have people ever Annoyed you by criticizing your drinking?____
    Have you ever felt bad or Guilty about your drinking?____
    Have you ever had a drink first thing in the morning to steady your nerves or get rid of a hangover? ____(Eye-opener) (if yes to any of above, cannot participate)

APPENDIX C
DSM-IV CHECKLIST

Subject # ________

Meets criteria: YES NO

Check any of the following symptoms if
(1) **it has been present during the same 2-week period**
(2) **it represents a change from previous functioning**
(3) **it is not due to a general medical condition**

(Must have five or more of symptoms below to warrant diagnosis of major depression; at least one of the symptoms must be depressed mood or diminished pleasure.)

____ depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g. feels sad or empty) or observation made by others (e.g. appears tearful).

____ markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others).

____ significant weight loss when not dieting or weight gain (e.g. a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day.

____ insomnia or hypersomnia nearly every day.

____ psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).

____ fatigue or less of energy nearly every day.

____ feelings or worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being depressed).

____ diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).

____ recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

1. The symptoms do not meet criteria for a Mixed Episode _______
2. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning _______

3. The symptoms are not due to the direct physiological effects of a substance (e.g. substance abuse or medication) or a general medical condition _______

4. The symptoms are not better accounted for by Bereavement _______

APPENDIX D
SUBJECT CHARACTERISTICS QUESTIONNAIRE

Subject # ______

1. Please list the medications that you are currently taking, including the dosage of each one and how long you have been taking it.

	Medication	Dosage	Length of time on medication
a.	____________________	______	__________________________
b.	____________________	______	__________________________
c.	____________________	______	__________________________
d.	____________________	______	__________________________
e.	____________________	______	__________________________

2. Did you take any pain medication today? _________ If yes, what did you take and at what dosage?________________________

3. When were you first diagnosed with Fibromyalgia? ____________

4. When did you start experiencing the symptoms of Fibromyalgia? ____________________

5. Do you feel as if you "hurt all over"? _______

6. Do you experience general fatigue? _______

7. Do you awaken in the morning feeling refreshed? _______

8. Do you tend to feel anxious or tense? _______

9. Do you have irritable bowel syndrome? _______

APPENDIX E
TIME-OF-TESTING VISUAL ANALOGUE SCALE

Subject # _______

1. Please rate the level of fatigue you are experiencing now:

None

Most Severe Fatigue
Imaginable

2. Please rate the level of pain you are experiencing now:

None

Most Severe Pain
Imaginable

3. Please rate the level of malaise (flu-like symptoms) you are experiencing now:

None

Most Severe Malaise
Imaginable

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